Antacid therapy of peptic ulcer

Part I A mathematical definition of an adequate dose

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EDITORIAL SYNOPSIS Because all the parameters needed to calculate an adequate dose of antacid for patients with peptic ulcer will probably never be known before treatment, a mathematical method is presented of calculating the minimum dose using the data of various authors as regards gastric secretion and emptying. Also studied is the effect of antacids on secretion rate and emptying time. It was found that to be effective in 90% of patients, a dose of 50 mEq. neutralizing capacity is adequate for male duodenal ulcer patients and of 26 mEq. for female duodenal ulcer or male gastric ulcer patients. If the patient's basal secretion is known, a dose of neutralizing capacity eight times the secretion rate is adequate.

In part II the neutralizing capacity of all available antacids is assessed as regards the amount of acid required to titrate a known amount of antacid to pH 4.5. From this information, the approximate dose of each antacid required to produce effective neutralization of gastric juice in the treatment of peptic ulcer has been determined and summarized in the tables for the antacids commonly used in treatment. The doses recommended are larger than those in routine use.

Although the first part of the paper may be of limited usefulness the second has great practical value and draws attention to the effectiveness or otherwise of many commercial preparations.

The treatment of peptic ulceration is based on bed rest and various methods of inhibiting peptic digestion; the latter include cessation of smoking, the use of anticholinergic drugs, and antacid therapy. The effect of smoking on gastric secretion and the course of peptic ulceration has been determined (Doll, Jones, and Pygott, 1958; Piper and Raine, 1959) and the inhibitory effect of anticholinergic drugs has been demonstrated by many workers. Anticholinergic drugs alone, however, do not influence the acid and pepsin concentration of gastric juice, though the output of both is decreased. Consequently, antacid therapy plays an essential part in the treatment of peptic ulcer. However, the dosage of antacids is undoubtedly the least accurately based of all the therapeutic measures mentioned. This is due to the great variations of the three variables that predominantly determine antacid dosage, namely, gastric secretion, gastric emptying, and the neutralizing capacity of antacids. The first part of this paper attempts to determine mathematically the antacid dosage required in the treatment of peptic ulcer, based on the data of gastric secretion of Bruce, Card, Marks, and Sircus (1959) and of Sun and Shay

(1957) and the emptying rates of Hunt and Spurrell (1951) and of Hunt (1959).

A SIMPLE MATHEMATICAL MODEL OF GASTRIC NEUTRALIZATION OF ANTACID *IN VIVO*

It is established that the stomach empties exponentially (Hunt and Spurrell, 1951; Hunt, 1959). The fractional rate of removal of antacid, as well as secreted acid, on a meal is constant. The basal gastric secretion is constant in a given patient to a good approximation, but differs between males and females and in cases of gastric and duodenal ulcer (Table I). There is no evidence that gastric secretion and emptying are systematically quantitatively related. The effects of uneven mixing of antacid on any rhythmic gastric actions are ignored in this approximate treatment. These and the effect of a meal are considered in the discussion.

Let $r(t)$ = the amount of antacid present in the stomach at time t ,

κ = emptying rate constant of excess antacid,

$t_{\frac{1}{2}}$ = $\ln 2/\kappa$ = half-time of emptying,

τ = 'starting index' or time after administration of antacid when exponential emptying rate commences (Hunt and Spurrell, 1951),

and s = rate per unit time at which antacid is neutralized by acid secreted by the stomach.

The rate of change of excess antacid at the time t is given by the simple differential equation

$$\frac{dr(t)}{dt} = -\kappa r(t) - s \quad (1)$$

which when integrated yields the solution

$$r(t) = e^{-\kappa(t-\tau)} \left(r_\tau + \frac{s}{\kappa} \right) - \frac{s}{\kappa} \quad (2)$$

where $r(t) = r_\tau$ at time $t = \tau$. If the stomach behaves as though the exponential emptying rate commenced before $t = 0$ then τ is considered to be negative (Hunt and Spurrell, 1951).

The amount of excess antacid, r_τ , which must be present at time $t = \tau$ to ensure that at a later time $t = T$ there will be no deficiency of antacid is found from equation (2) to be

$$r \geq \frac{s}{\kappa} (e^{\kappa(T-\tau)} - 1) \quad (3)$$

and thus at time $t = 0$, when antacid is actually administered, the amount to be added to the stomach completely to neutralize gastric acidity until time $t = T$ is

$$r_0 \geq \frac{s}{\kappa} (e^{\kappa(T-\tau)} - 1 + \tau\kappa) \quad (4)$$

DERIVATION OF AMOUNT OF ANTACID NECESSARY TO TREAT ADEQUATELY PATIENTS OF UNKNOWN GASTRIC FUNCTION

Without knowledge of the patient's gastric secretion and emptying rates the precise quantity of antacid, r_0 , just to treat adequately the patient cannot be defined. However, utilizing the known range of secretion and emptying rates encountered in cases of peptic ulcer a dose of antacid can be defined which will reduce the gastric acidity to zero in any desired fraction of patients being treated. Thus, for example, a dose which will always adequately treat 90% of patients can be established. The ranges of basal secretion and emptying rate reported in the literature are summarized in Table I.

In order to assign the antacid dosage, r_0 , which will adequately treat any desired fraction of patients, it is needed to establish the statistical distribution of r_0 . Given the statistical distributions of s , $t_{1/2}$, and τ , it is in principle possible to derive that of r_0 using equation (4). For any reasonable assumption of distributions consistent

with the data which Table I summarizes, however, the distribution of r_0 was found to be inexpressible in terms of known mathematical functions. A numerical approach was therefore indicated.

Normal distributions were fitted to the data of $t_{1/2}$, τ , and s , using the means and standard deviations listed in Table I. It was assumed that $t_{1/2}$, τ , and s were statistically independent since there was no consistent evidence to the contrary. A Monte Carlo or model sampling calculation was performed to obtain the distribution of r_0 by the random sampling of values of $t_{1/2}$, τ , and s and the use of equation (4). One thousand sets of values of $t_{1/2}$, τ , and s were sampled corresponding to the calculation of r_0 for 1,000 hypothetical patients. The samples on which the data for $t_{1/2}$, τ , and s were based were not large enough to justify a calculation with a larger number of hypothetical patients. The process was performed three times, once for male duodenal ulcer patients, once for female duodenal ulcer patients, and finally for male gastric ulcer patients. The distributions were calculated with $T = 1$ in equation (4), corresponding to the amount of antacid required to neutralize gastric acidity for one hour.

From these distributions the amount of hourly administered antacid necessary adequately to treat 90% of male duodenal ulcer patients is found to be 50 mEq. It is emphasized that this amount of antacid does not effect a 90% reduction of gastric acidity in all patients, but more importantly, reduces the acidity to zero in 90% of patients. For female duodenal ulcer patients and male gastric ulcer patients the corresponding amount is 27 mEq. and 26 mEq. respectively. These and other amounts of antacid are listed in Table II.

TABLE II
AMOUNT OF HOURLY ADMINISTERED ANTACID TO REDUCE GASTRIC ACIDITY TO ZERO IN X% OF PATIENTS

Lesion	Sex	x%		
		10% (mEq.)	50% (mEq.)	90% (mEq.)
Duodenal ulcer	Male	6.7	18.6	49.8
	Female	3.1	10.0	26.7
Gastric ulcer	Male	3.3	9.6	25.6

TABLE I
VALUES OF BASAL SECRETION AND EMPTYING RATE REPORTED IN THE LITERATURE

	Mean	S.E.	S.D.	Range	No. of Cases	Reference
<i>Basal gastric secretions (mEq./hr.)</i>						
Duodenal ulcer (male)	6.0	—	—	0.1-23.1	176	Bruce <i>et al.</i> (1959)
	5.7	—	—	—	38	Sircus (1960)
	4.39	0.51	2.18	1.91-9.42	18	Sun and Shay (1957)
	3.2	0.55	2.5	—	21	Littman (1957)
(female)	3.2	—	—	0.1-14.9	61	Bruce <i>et al.</i> (1959)
Gastric ulcer (male)	3.1	—	—	0.0-16.4	20	Kay (1953)
	2.1	—	—	0.1-14.4	40	Bruce <i>et al.</i> (1959)
	1.2	—	—	0.0-7.9	40	Bruce <i>et al.</i> (1959)
(female)	—	—	—	—	—	—
<i>Gastric emptying (min.)</i>						
Starting index, τ	— 0.5	2.00	9.6	— 15.3-17.3	23	Hunt and Spurrell (1951)
Half-time of exponential emptying, $t_{1/2}$	21.8	1.27	6.1	9.0-30.1	23	Hunt and Spurrell (1951)

FIG. 1. Antacid dose required to treat 10%, 50%, and 90% of patients with varying secretion rates.

If nothing is known of the patient's gastric function these hourly antacid doses of 50, 27, or 26 mEq. are the indicated dosages in the medical treatment of peptic ulcer.

DOSAGE WHEN SECRETION RATE IS KNOWN

The measurement of emptying rate is a moderately time-consuming procedure (Hunt and Spurrell, 1951) and is rarely performed in clinical practice. The basal secretion, however, is known in many, if not most patients, and with knowledge of its value and the known range of emptying rates, doses of antacid adequate to

TABLE III

PERCENTAGE OF PATIENTS WITH VARYING SECRETORY RATES ADEQUATELY TREATED BY ANTACID DOSES OF 25 MEQ. AND 50 MEQ. ADMINISTERED HOURLY

Secretion Rate (mEq./hr.)	Percentage Adequately Treated by Hourly Antacid Dose of	
	50 mEq.	25 mEq.
1.0	98.8	97.7
5.0	93.8	79.3
10	78.9	31.0
15	54.8	5.5
20	31.2	1.0
25	13.6	1.0
30	5.7	< 1.0
Male duodenal ulcer	90.0	66.2
Female duodenal ulcer	96.0	88.6
Male gastric ulcer	97.0	88.2

treat any desired fraction of patients with a given secretion rate can be defined. These are depicted in Fig. 1 where for any given secretion rate, s , an hourly dose equal to that indicated by the upper line will reduce the gastric acidity to zero in 90% of patients with this s . A dose equal to that indicated by the middle line adequately treats 50% of patients, and that indicated by the lower line treats adequately but 10% of patients.

If the patient's basal secretion is measured, Fig. 1 depicts the indicated hourly dosage of antacid, which varies from 7.8 to 224 mEq. for secretion rates varying from 1 to 30 mEq./hr. As will be seen when Part II is read, it is convenient to think of the efficiency of antacids in terms of neutralizing capacity of 25 and 50 mEq. Table III shows the percentage of patients adequately treated by these doses given hourly to patients with varying secretory rates.

EFFECT ON REQUIRED ANTACID DOSE OF CHANGES IN EMPTYING RATE AT CONSTANT SECRETION RATE AND VICE VERSA

Using equation (4) the variation in the required hourly antacid dosage may be observed as either emptying rate or secretion rate is varied, the other being held constant (Table IV). On those rare occasions when information on both secretion and emptying rate is available for a patient, the indicated dose may be taken by extrapolation from Table IV, or more exactly, by substitution into equation (4). In either case approximate allowance for the observational error in the measured parameters may be made by adjusting each parameter by 2 standard deviations before entering the table or substituting in the equation.

TABLE IV

EFFECT OF VARIATION IN SECRETION AND EMPTYING RATES ON DOSE OF ANTACID REQUIRED HOURLY (mEq.)

Emptying Rate		Secretion Rates (mEq./hr.)				
Half-time ($t_{\frac{1}{2}}$ min.)	Starting Index (t min.)	0.1	1.0	5.0	10.0	20.0
30	15	0.16	1.57	7.9	15.7	31.4
25	7.5	0.21	2.11	10.5	21.1	42.2
20	0	0.34	3.38	16.9	33.8	67.7
15	- 7.5	0.77	7.70	38.5	77.0	154
10	-15	4.36	43.6	218	436	872

EFFECT OF FREQUENCY OF ADMINISTRATION OF ANTACID

In the previous sections of the paper an hourly dose has been uniformly calculated. This was for reasons now made clear and further considered in the discussion.

Using equation (4) the required dose of antacid can be calculated as a function of the frequency of administration for any given gastric function specified by values of $t_{\frac{1}{2}}$, τ , and s . In Table V the dose is described for each of three ulcer patients with low, average, and high secretion and emptying rates.

It is demonstrated that, except for a high secretion rate combined with a rapid emptying, the total amount

TABLE V
EFFECT OF FREQUENCY OF ADMINISTRATION OF ANTACID ON DOSAGE REQUIRED FOR
ADEQUATE TREATMENT OF PEPTIC ULCER BY COMPLETE NEUTRALIZATION OF ACIDITY

Gastric Function	Continuous Infusion	Frequency of Dose						
		Quarter Hour	Half Hour	One Hour	Two Hours	Three Hours	Four Hours	Six Hours
<i>Low secretion and emptying rate</i> s = 1.0 mEq./hr.; t _½ = 30 min.; τ = 15 min.								
Amount per dose (mEq.)	—	0.25	0.55	1.57	7.71	32.3	131	2,100
Total amount administered each 12 hours (mEq.)	12	12	13.2	18.8	46.3	129	393	4,200
<i>Moderate secretion and emptying rate</i> s = 5.0 mEq./hr.; t _½ = 20 min.; τ = 0 min.								
Amount per dose (mEq.)	—	1.64	4.40	16.9	153	1,250	10,100	659 × 10 ³
Total amount administered each 12 hours (mEq.)	60	78.7	106	203	918	5,000	30,300	1,320 × 10 ³
<i>High secretion and emptying rate</i> s = 10.0 mEq./hr.; t _½ = 10 min.; τ = 15 min.								
Amount per dose (mEq.)	—	14.3	49.7	436	28,600	1,860 × 10 ³	121 × 10 ⁶	510 × 10 ⁹
Total amount administered each 12 hours (mEq.)	120	686	1,190	5,230	172,000	7,440 × 10 ³	363 × 10 ⁶	1,020 × 10 ⁹
s = secretion rate; t _½ = half-time of emptying = $\frac{\ln 2}{\kappa}$ where κ is the exponential emptying rate constant; τ = starting index.								

s = secretion rate; $t_{1/2}$ = half-time of emptying = $\frac{\ln 2}{\kappa}$ where κ is the exponential emptying rate constant;
 τ = starting index.

administered over a 12-hour period is clinically acceptable if the doses are administered hourly or more frequently. Doses administered two hourly or less frequently involve amounts of antacid over a 12-hour period which are unacceptable in practice, except in patients with low secretion and emptying rates. While the administration of half-hourly doses, or preferably a continuous administration, is without doubt a superior technique, a compromise regimen involving hourly doses would generally prove to be more practical for most patients and supervising medical staff. If the correct dosage scheme is followed the gastric acidity in 90% of patients is still held rigidly to zero.

CONTINUOUS ANTACID ADMINISTRATION As the frequency of administration is increased the required dose approaches the secretion rate asymptotically. Thus in Table IV the adequate doses per hour, if given by continuous administration, are 1, 5, and 10 mEq. respectively, compared with 1.57, 16.9, and 436 mEq. for an hourly administration. Continuous administration is thus of practical value for patients with high secretion and emptying rates.

COMPARISON OF CALCULATED ANTACID DOSAGE WITH EXPERIMENTAL RESULTS *IN VIVO*

The results of the calculations described in this paper were compared where possible with corresponding experimental findings. The amount of sodium bicarbonate necessary to maintain the pH of gastric contents at or above 4 when given by continuous infusion in a milk drip has been described (Price and Sanderson, 1956). Basal secretion or

emptying rate values were not given for the group studied but should be typical of those usually obtained. The calculated and experimental values are compared in Table VI, where for the purpose of comparison 1 g. of sodium bicarbonate is considered to have a neutralizing capacity of 11.5 mEq. *in vitro*.

The calculated doses, while much greater than those traditionally used in the treatment of peptic ulcer, are in general agreement with the experimental values. The calculated doses, being somewhat lower than the experimental values, may reflect inadequate mixing of the antacid when given experimentally by continuous infusion, thus necessitating a larger dose to neutralize a given amount of acid. Alternatively,

TABLE VI

COMPARISON OF AMOUNT OF ANTACID REQUIRED PER HOUR
IN TREATMENT OF MALE DUODENAL OR GASTRIC ULCER AS
DETERMINED EXPERIMENTALLY (PRICE AND SANDERSON,
1956) WITH THAT CALCULATED IN THIS PAPER

	Antacid Dose Per Hour (mEq.)	
	Duodenal Ulcer	Gastric Ulcer
Experimental continuous infusion, 15 patients:		
Greatest dose	67.1	76.7
Average dose	45.5	20.5
Least dose	28.7	9.6
Calculated hourly dose needed to treat:		
90% of patients	49.8	25.6
50% of patients	18.6	10.0
10% of patients	6.7	3.3

inadequacies in the mathematical model employed in the theoretical analysis, especially if the medians of the distributions of secretion rates greatly exceed the respective means reported in the literature, would result in the calculation of a falsely low antacid dose.

DISCUSSION AND CONCLUSIONS

All the parameters needed to calculate the adequate dose of antacid will probably never be known in most cases of peptic ulcer before treatment; some of the techniques, such as the measurement of emptying rate and starting index, are moderately time-consuming procedures (Hunt and Spurrell, 1951). The basal secretion, however, is known in many, if not most patients, and with knowledge of its value and the observations of other workers on emptying rates and starting indices, an approximation of the antacid dosage can be obtained (Fig. 1). If no information at all is available an approximate dose can be determined based on statistical data as in Table II. The calculated doses listed in both the Figure and Table II are those required to neutralize basal secretion and do not take into consideration the secretory response to frequent meals that further increase gastric secretion and consequently the required dose of antacid. It is obvious from Table V that doses of antacid must be given at least hourly if any effect is to be produced by commonly used doses.

It is emphasized that while the adequacy of the mathematical model here employed to describe the secretion into and emptying from the stomach is well established in the literature, there is wide variation in the values of the different parameters

in various reports (Table I), and thus the calculated doses of antacid are approximate only. The independence of the half-time of gastric emptying and the starting index, assumed in some calculations above, may not be strictly true and would also affect the calculated antacid dosage. Inadequate mixing of antacid is a further unpredictable factor influencing the required dose of antacid. Any rhythmic gastric actions would introduce further uncertainties, since for given average basal secretion and emptying rates the dose required would vary according as the time of administration was related to the commencement of the cyclic periods. Notwithstanding these uncertainties, the general agreement in antacid requirement between the study of Price and Sanderson (1956) *in vivo* and this mathematical study using data from the literature confirms the general validity of the conclusions.

It is emphasized that the dosage determined in the above calculations is minimum dosage. The stimulation of gastric secretion by meals would necessitate increased antacid dosage, and it is possible that gastric secretion and emptying may not be independent variables, and those patients with high secretion rates may have rapid emptying rates, thereby increasing dosage of antacid.

We believe that the minimum antacid doses are as follows: If no information is available on the patient's gastric function, then a dose of 50 mEq. once hourly is adequate for duodenal ulcer in a man, 26 mEq. for duodenal ulcer in a woman or gastric ulcer in a man. If the patient's basal secretion rate is known, a dose of neutralizing capacity eight times the secretion rate should suffice in most cases, if given hourly.

Part II An evaluation of antacids *in vitro*

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In this part of the paper we assess the neutralizing capacity *in vitro* of a series of antacids and determine the approximate dose of each required in the treatment of peptic ulcer.

METHOD

The method used differed from that of previous studies (Johnson and Duncan, 1945; Hammarlund and Rising, 1949; Dale and Booth, 1955) in that a known amount of antacid preparation was added to 25.0 ml. of distilled

water and titrated to pH 4.5 with N_{10} HCl solution at room temperature. For these determinations an autotitrator (Radiometer) was used; the autotitrator was regulated to a delay in shut-off of five seconds (which meant the reaction mixture had to retain the desired pH (4.5) for at least five seconds). When powders were used 40 mg. was mixed in 25 ml. of distilled water, when a liquid preparation was used 4 ml. was made up to 25 ml. in distilled water, and when a tablet preparation was assessed the whole tablet was placed in 25 ml. of distilled water; when tablets were investigated the neutralizing