

Validity of polyethyleneglycol in the study of the total pancreatic secretion in man after stimulation by secretin, pancreozymin, or food

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EDITORIAL COMMENT Calculations of rate of flow can be misleading on account of incomplete mixing or distribution across the transverse section of the intestine. This error is minimized when there is increased muscular activity.

Experimental studies in anaesthetized animals have shown that calculation of the intestinal flow by means of infusion of unabsorbable markers may be misleading to a varying degree (Jacobson, Bondy, Broitman, and Fordtran, 1963; Worning and Amdrup, 1965; Worning, Amdrup, and Henriksen, 1966).

It is the aim of the present study to define whether the intestinal flow, *i.e.*, the amount of fluid which during a given time passes a given section of the intestine, might be determined in the intact human intestinal tract by the marker technique, thereby obtaining an expression of the rate of secretion of pancreatic enzyme after stimulation of the pancreatic secretion by secretin, pancreozymin, or food.

METHODS

The duodenum was intubated by means of a double tube composed of two polyvinyl tubes (external/internal diameter 2.3/2.1 mm.). The terminal 5 cm. of the longer tube was provided with eight perforations in the wall; the shorter tube was tied to the longer one 10 to 20 cm. orally to the perforations. When the tip of the longer tube reached the ligament of Treitz, and that of the shorter was at least 5 cm. distally to the pylorus, the tubes were fixed to the cheek of the subject. In all cases the position of the tubes was checked radiologically.

Polyethyleneglycol 4000 (P.E.G.), dissolved in physiological saline, served as marker.

Throughout the whole experiment the marker solution was infused at a constant rate through the shorter tube

while the intestinal content was simultaneously recovered by simple siphonage through the longer tube. The infusion rate varied between 0.6 and 2.5 ml./min. in the different experiments.

After a preliminary period covering 20 to 30 minutes, the pancreatic secretion was stimulated by secretin (Lilly or Vitrum), 1 u/kg. intravenously, or by pancreozymin (Boots or Cecekin, Vitrum), 1 u/kg. intravenously, or by an orally administered fluid meal consisting of 45 g. of skimmed milk powder supplemented by corn oil and 20 g. glucose, all dissolved in 300 ml. of water.

Subsequently the intestinal content was aspirated for 60 or 80 minutes subdivided into 20-minute intervals.

In the cases in which secretin or pancreozymin were used as stimulants, the gastric juice was aspirated by means of intermittent, mechanical suction at negative pressure of 50 to 100 mm.Hg through a separate tube inserted distally into the stomach.

The aspirated intestinal content was measured, and the concentrations of P.E.G. and of amylase were determined in the individual aspirates. Polyethyleneglycol was determined according to Hyden's method (1955), and α -amylase was determined according to Dahlqvist's method (1962) with minor modifications (Worning and Müllertz, 1966).

Using the following symbols, rate of infusion of marker solution = v ml./min., concentration of marker in the solution = a mg./ml., volume aspirated during the time $t = r$ ml., concentration of marker in $r = b$ mg./ml., concentration of α -amylase in $r = c$ U./ml., the integrated intestinal flow (I.I.F.) = the volume passing the site of aspiration in a given time t can be calculated as (I.I.F.) = $v t a/b$ ml.

The integrated endogenous intestinal flow is during the same period = (I.I.F.) - $v t$ ml. The recovery of marker is calculated as $100 r b/v t a$ per cent, and the total secretion of amylase as (I.I.F.) c .

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TABLE I

RECOVERY OF INFUSED MARKER (P.E.G.) AS PERCENTAGES OF INFUSED AMOUNTS IN THE FASTING STATE AND AT DIFFERENT INTERVALS AFTER STIMULATION OF THE PANCREATIC SECRETION

Stimulant		Period					
		Fasting	0-20 Minutes	20-40 Minutes	40-60 Minutes	60-80 Minutes	80 Minutes
Secretin	n		9	9	9	9	9
	Mean		32.4	13.3	8.6	17.9	18.1
	Range		0-100	0.54	0.26	0.57	4.41
Pancreo- zymin	n		8	8	8	6	8
	Mean		15.9	13.0	12.0	34.2	18.1
	Range		2.45	0.45	0.28	0.100	6.35
Standard meal	n		15	15	15	15	16
	Mean		29.5	16.1	23.7	22.3	21.4
	Range		0.74	0.48	4.75	0.79	3.53
All	n	19	32	32	32	30	33
	Mean	22.5	27.0	14.6	16.6	23.3	19.8
	Range	3.68	0.100	0.54	0.75	0.100	3.53

n = number of observations

MATERIAL

The examinations were carried out by a uniform technique on 33 inpatients; secretin was used as stimulant on nine occasions (in eight subjects), pancreozymin on eight occasions (in the same eight subjects); a fluid meal composed of skimmed milk powder with corn oil and glucose dissolved in water served as stimulant on 16 occasions.

RESULTS

RECOVERY OF INFUSED MARKER Table I illustrates the recovery of marker substance, recorded as mean value and observed ranges. The apparently different mean recoveries following one or the other stimulant were not statistically significant, nor did recovery alter significantly during the period of aspiration. The individual variations of recovery were quite appreciable and, within the individual subject, recovery might vary considerably from one 20-minute period to the next. With the technique used here, recovery amounted merely to about 20%.

CALCULATED INTESTINAL FLOW Table II records the mean values for the integrated endogenous intestinal flow obtained in the four 20-minute periods following stimulation of the pancreatic secretion. Figures represent observations obtained exclusively in subjects without symptoms or signs of gastrointestinal disorders. Figure 1 shows the equivalent individual values. Irrespective of the stimulant used, the calculated integrated endogenous intestinal flow showed considerable inter-period variations in the individual subject. The inter-subject variations were marked, especially after stimulation

TABLE II

CALCULATED INTEGRATED ENDOGENOUS INTESTINAL FLOW AT DIFFERENT PERIODS AFTER STIMULATION OF THE PANCREATIC SECRETION (ML./20 MIN.)

Stimulant		Period			
		0-20 Minutes	20-40 Minutes	40-60 Minutes	60-80 Minutes
Secretin	n	5	5	4	6
	Mean	117.0	187.6	129.8	147.5
Pancreo- zymin	n	5	4	3	2
	Mean	116.2	124.8	91.3	56.5
Standard meal	n	6	6	6	5
	Mean	93.6	226.0	124.2	117.8

n = number of observations

by secretin or pancreozymin (Fig. 1). Following secretin, the intestinal flow was, on an average and in all subjects, calculated to the highest value in the second 20-minute period (Table II, Fig. 1A). Mean values in the periods 40-60 and 60-80 minutes after secretin were higher than that recorded for the initial 20-minute period (Table II).

Only small differences between the integrated endogenous intestinal flow following secretin and pancreozymin were apparent in the initial two periods. Following stimulation by secretin or food, the total would, on an average, be about 500 ml./80 min.; after stimulation by pancreozymin it would be 400 ml./80 min.

CALCULATED SECRETION OF AMYLASE Table III records the mean values of the calculated total secretions of amylase during 20-minute intervals, expressed in kilounits (kU). The table includes

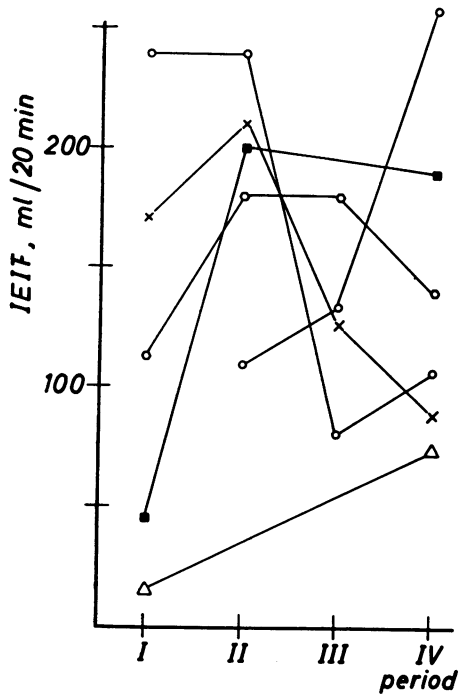


FIG. 1a

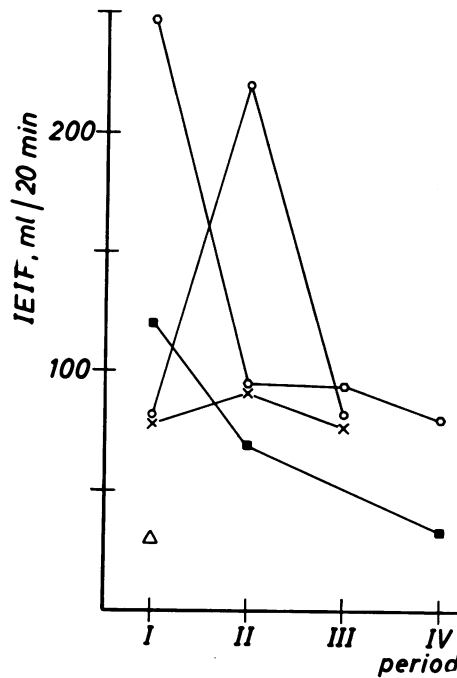


FIG. 1b

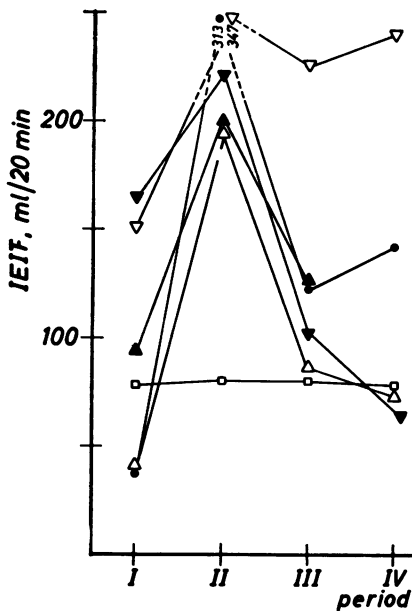


FIG. 1c

FIG. 1. The integrated endogenous intestinal flow (I.E.I.F.), calculated on the basis of the concentration of marker in aspirates in four 20-minute periods after stimulation of the pancreatic secretion by (A) secretin (Lilly), (B) pancreozymin (Boots), (C) food.

values exclusively obtained in subjects without gastrointestinal disorders. The equivalent individual values are seen in Figure 2. Variations between amounts secreted in the different periods in the individual subjects, as well as variations from one subject to another, were appreciable here too. In general the calculated values for secretion of amylase varied in parallel with that for the integrated endogenous intestinal flow (Figs. 1 and 2). The mean values in the two initial periods were nearly identical following secretin and pancreozymin, being more excessive after a meal (Table III).

TABLE III

CALCULATED SECRETION OF AMYLASE IN DIFFERENT PERIODS AFTER STIMULATION OF THE PANCREATIC SECRETION (ku IN 20 MIN.)

Stimulant	n	Period			
		0-20 Minutes	20-40 Minutes	40-60 Minutes	60-80 Minutes
Secretin	5	5	3	6	
	Mean	12.150	13.852	8.463	12.122
Pancreo- zymin	5	4	2	2	
	Mean	10.100	12.765	14.150	6.265
Standard meal	6	6	6	5	
	Mean	14.360	26.440	15.964	16.022

n = number of observations

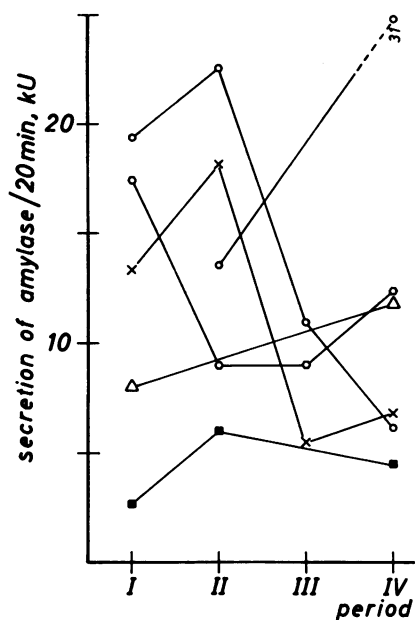


FIG. 2a

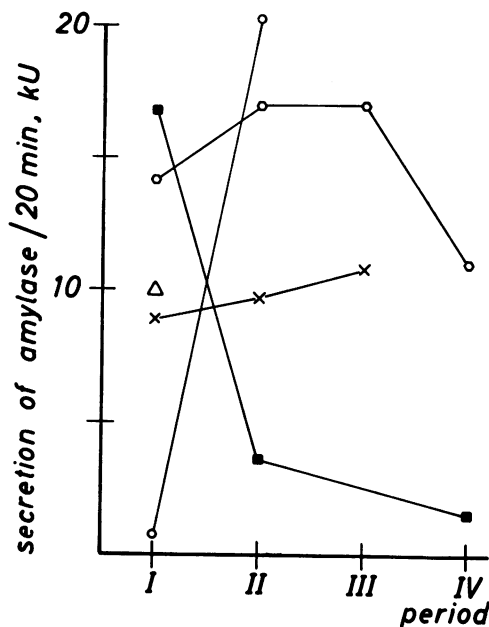


FIG. 2b

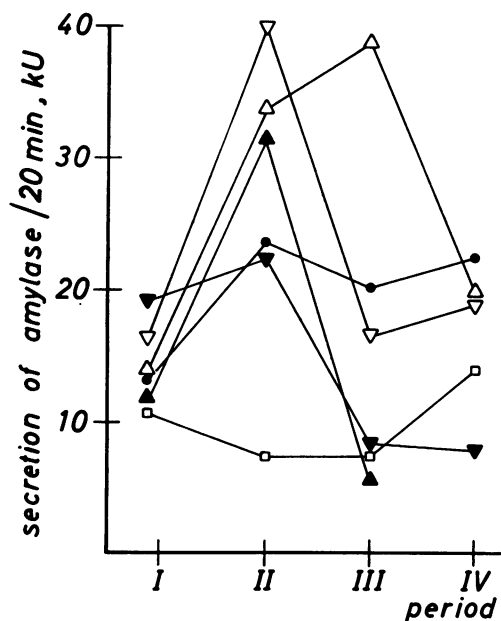


FIG. 2c

FIG. 2. The calculated secretion of amylase in four 20-minute periods after stimulation of the pancreatic secretion by (A) secretin (Lilly), (B) pancreozymin (Boots), (C) food.

In one subject, the integrated endogenous intestinal flow and the total secretion of amylase following stimulation by secretin was examined on two successive days. The reproducibility was very poor (Figs. 1A and 2A).

DISCUSSION

According to the recovery experiments, quantitative recovery of the intestinal contents represents the exceptions when the technique discussed here was used. The fluctuating recovery in the individual subject indicated that the part of the intestinal flow to be aspirated varied considerably from one period to the next.

The calculated values for intestinal flow and pancreatic enzyme secretion were in many respects incompatible with the present knowledge of the pancreatic function.

Numerous clinical investigations have shown the secretin-released secretion, estimated by means of aspiration from the distal part of the duodenum, to be most intense during the initial 10 to 20 minutes following the injection, after which it gradually subsides (Voegtlin, Greengard, and Ivy, 1934; Ågren and Lagerlöf, 1936; Diamond, Siegel, Gall, and Karlen, 1939; Lagerlöf, 1942; Dornberger, Comfort, Wollaeger, and Power, 1948; Pfeffer, Stephenson, Jr., and Hinton, 1952; Dreiling, 1955; Burton, Evans, Harper, Howat, Oleesky, Scott, and

Varley, 1960; Dreiling and Janowitz, 1962; Lagerlöf, Ek and Nyberg, 1962; Correia and Barros, 1963; Christensen, 1963). Cases with the largest aspirates in the second 20-minute period following the injection of secretin have been recorded (Lake, 1947; Cathalan, Charmot, and Pujo, 1961; Gülzow and Arendt, 1964), but values in the periods 40-60 and 60-80 minutes exceeding those obtained in the initial 20 minutes have never been observed.

The mean value for the calculated integrated endogenous intestinal flow following secretin (500 ml./80 min.) exceeded by far the volumes aspirated from the distal duodenum following stimulation by secretin in a similar dose. Dreiling (1955) recorded a mean value of 200 ml./80 min., and Rosenberg, Friedland, Janowitz, and Dreiling (1966) recorded a value of 230 ml./80 min. Higher values have not been recorded.

The lack of differences between mean values for the integrated endogenous intestinal flow and amylase secretion in the initial two periods after secretin and pancreozymin are in contradistinction to the physiological action of secretin as a specific stimulant to the secretion of fluid and bicarbonate (Janowitz and Dreiling, 1962) and pancreozymin as a specific stimulant to the secretion of enzyme (Harper, Blair, and Scratcherd, 1962). The decreasing values for the integrated endogenous intestinal flow and, to a minor degree of amylase secretion, in the later periods following pancreozymin are in fair accord with the short time of action of injected pancreozymin (Werner and Mutt, 1954; Dreiling and Janowitz, 1962; Hanscom and Littman, 1963).

The results obtained after stimulation by a meal are conflicting and difficult to interpret.

Hunt and MacDonald (1954) and Borgström, Dahlqvist, Lundh, and Sjövall (1957) have shown the rate of gastric emptying after meals of the type and size used here to be fairly constant except for the initial period, when the rate of emptying is slower.

Pincus, Thomas, Hausman, and Lachman (1948), Annis and Hallenbeck (1952), and Henriksen and Worning (unpublished data) demonstrated in dogs that the pancreatic secretion of fluid as well as of enzyme increased immediately after food, a feature also seen in human subjects suffering from pancreatic fistula (Hölsti, 1913; Mocquot, Joltrain, and Landat, 1933; Turai, Vintila, Cosmulesco, Soare, and Stanesco, 1961). After the initial rise, however, the secretion remains fairly constant for a long time.

Worning and Müllertz (1966) observed that the concentrations of different pancreatic enzymes in aspirates from the human duodenum were highest in the initial 20 minutes after ingestion of a fluid meal. In the subsequent hour the concentrations remained constant at a lower level.

Thus, there is every possibility that the endogenous flow through the duodenum, and the secretion of enzyme from the pancreas, increase from the first to the second 20-minute period after intake of food and then remain constant at least for an hour.

In the initial two periods, the calculated values for the integrated endogenous intestinal flow and for secretion of amylase were on an average (Tables II and III) and in nearly all subjects (Figs. 1C and 2C) in fair accord with the expected values. In the same two periods the inter-subject variations were limited. In the last two periods the inter-subject variations and the discrepancies between calculated and expected values were considerable. In one subject, the calculated values for the integrated endogenous intestinal flow and for amylase secretion differed markedly from values obtained in the other subjects (Figs. 1C and 2C).

Irrespective of the stimulant applied discrepancies between the calculated and the expected integrated endogenous intestinal flow were seen. If correct values are to be obtained with the technique used here regurgitation to the stomach of the infused marker must not take place. Furthermore, a uniform mixing of the marker in the intestinal contents is a necessary prerequisite.

The gastric aspirates obtained after stimulation by secretin or pancreozymin were not analysed for P.E.G. Thus, regurgitation to the stomach cannot be excluded. Lagerlöf (1942) and Dreiling and Hollander (1948) observed, however, that permanent aspiration of the duodenal contents prevented regurgitation to the stomach.

It has already been demonstrated (Worning and Amdrup, 1965) that infused marker is not uniformly distributed over the transverse section of the intestine, and this incomplete mixing of the infused marker in the intestinal contents is probably the main reason for the incorrect flow calculations. In general, the results obtained after ingestion of a meal were in better accord with the expected values than were the results obtained after stimulation by secretin or pancreozymin. This may be due to a more intense duodenal motility during digestion of the meal resulting in a more uniform mixing of the infused marker in the intestinal contents.

It is evident from the results obtained that the technique used here, involving permanent infusion of a nonabsorbable marker proximally into the intestine, fails to determine with sufficient accuracy the endogenous intestinal flow in the intact, human intestinal canal after stimulation of the pancreatic secretion by secretin or pancreozymin. Consequently, determination of the rate of enzyme secretion from the pancreas during a given period following stimulation is impossible.

The results obtained after ingestion of a meal were probably more reliable. The pronounced inter-subject variations in the later periods and the low values in one of the subjects indicate that misleading results were obtainable even after ingestion of a meal.

In the single subject it can hardly be decided whether the intestinal flow is estimated with sufficient accuracy or with a considerable error. Thus, the technique is not applicable for determination of the secretion rates of pancreatic enzymes in the single subject.

SUMMARY

Using infusion of a non-absorbable marker proximally into the duodenum, an attempt has been made to determine the intestinal flow, *i.e.*, the volume of fluid passing a definite intestinal section within a definite period, together with the coincident total amylase secretion from the pancreas after stimulation of the pancreatic secretion by secretin, pancreozymin, or food.

The calculated intestinal flow and the calculated values representing the total amylase secretion deviate appreciably from the expected values in the experiments using secretin or pancreozymin as stimulant.

In general, the deviations from the expected values were less pronounced after ingestion of a meal, but even here some of the results were misleading.

The technique used here has failed to provide a sufficiently exact calculation of the pancreatic secretion of amylase in a single subject.

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