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Chemical Antroneurolysis With and Without Highly Selective Vagotomy

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Because of the lower recurrence rate of ulceration when vagotomy is accompanied by antrectomy, we studied the effects of combining submucosal denervation of the antrum (antroneurolysis) with highly selective vagotomy (HSV). Chemical antroneurolysis (CANL) was performed by submucosal injection of 50% ethanol. In two gastric fistula dogs HSV produced a significant decrease in peak acid output (PAO) in response to 0.2 U/kg insulin (5.42 ± 0.46 → 3.32 ± 0.99 meq/15 min, $P < 0.06$). Subsequent CANL caused no further decrease in PAO (3.54 ± 0.52 meq/15 min). In three gastric fistula dogs, initial CANL yielded a slight increase in PAO (5.42 ± 0.46 → 7.30 ± 1.04 meq/15 min, $P < 0.01$). Subsequent HSV lowered PAO significantly below control (2.27 ± 0.74 meq/15 min, $P < 0.001$). Response to serial doses of betazole and pentagastrin was not significantly changed by any operation, except that CANL followed by HSV led to a decreased response to pentagastrin. Gastric motility, peristalsis, and emptying times were essentially unchanged. The response of four dogs with Heidenhain pouches to test meals was studied before and after CANL. Peak acid output following a test meal was not significantly changed (0.385 ± 0.078 → 0.392 ± 0.083, $P > 0.92$). CANL produced no change in maximum serum gastrin rise above basal in response to a test meal either in four pouch dogs (47.4 ± 2.54 → 40.9 + 3.69 pg/ml, $P > 0.13$) or in four normal dogs (27.5 ± 3.41 → 33.8 ± 4.47 pg/ml, $P > 0.16$). Basal gastrins were also unchanged. In conclusion, we feel that CANL provides no significant advantage over HSV, while increasing its complexity.

INTRODUCTION

Highly selective vagotomy (HSV) was developed in an attempt to reduce the side effects associated with truncal vagotomy and the different accompanying drainage procedures [1–3, 5, 14, 16, 18]. However, HSV has been noted by some to have a relatively high rate of recurrent ulceration, ranging from 6 to 22% [3, 13, 14, 16, 18]. HSV has been shown to raise both basal and stimulated gastrin levels [1, 4, 6, 15, 17], and this finding has been proposed as an explanation for the higher recurrence rate [11]. The elevated gastrin level has been variously attributed to reflex gastrin release stimulated by antral distension or to elevated pH secondary to decreased acid output following the vagotomy [1, 6]. The former reflex is believed to be mediated by both antral vagovagal and intramural cholinergic pathways, all of which are left intact in HVS [4, 6, 7, 19, 28]. Grotzinger showed that these gastrin releasing reflexes were suppressed by atropine after HSV, suggesting that they were cholinergically mediated [8]. Dragstedt and Woodward demonstrated the importance of these cholinergic mechanisms in dogs by chemically denervating the antrum with submucosal injection of 5% phenol [7, 28]. Schapiro has devised a method of submucosal denervation with various concentrations of ethanol which he has successfully applied to the canine antrum and fundus [19, 20–22]. The purpose of this study was to evaluate motility, acid secretion, and gastrin release in response to various stimuli before and after CANL alone and in conjunction with HSV.

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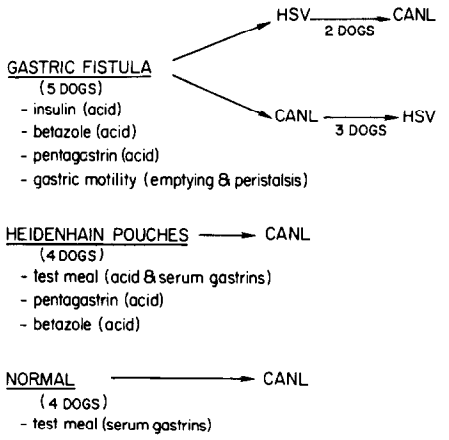

FIG. 1. Design of experiments. HSV indicates highly selective vagotomy and CANL represents chemical antroneurolysis. Designated studies were performed before and after each stage of the experiment.

METHODS

Surgery

Thirteen mongrel dogs weighing between 10 and 25 kg were used (Fig. 1). All dogs were fasted 24 hr before operation, and all operations were done under general halothane anesthesia, except HSV which was performed with sodium pentobarbital and continuous positive pressure ventilation.

1. Heidenhain pouches (HP). These were constructed in four dogs as denervated fundic pouches with volumes of about 50 ml. The pouches were drained by Gregory cannulas brought through stab wounds in the left lateral abdominal wall.

2. Gastric fistulas (GF). These were created in five dogs by interposing a 12-cm segment of reversed jejunum between the posterior gastric wall and the left flank, where the proximal end of the jejunum was brought through the skin and sutured to a circular opening in the skin. All fistulas were continent and easily admitted a No. 18 sump tube for gastric sampling.

3. HSV. The antral branches of the crow's foot of the nerves of Latarjet were located and preserved along with the main vagal trunks. The remaining branches of the anterior and posterior vagus along the lesser curvature were divided and ligated. The dissection was continued superiorly to about 6 cm above the gastroesophageal junction, a procedure which required entering both pleural spaces in each instance [9, 11].

4. CANL. A 6-cm gastrotomy was made in the anterior wall of the antrum. Through this, 50% ethanol was injected submucosally so that a bleb was raised over the entire antrum from 1 cm beyond the pylorus to about 2 cm proximal to the incisura [19].

Experiments

All dogs were fasted for 24 hr prior to an experiment. No experiments were conducted within 3 weeks of an operative procedure and the overall experimental design is depicted in Fig. 1. All studies were done in the same room at approximately the same time of day. Serum gastrin values were determined by Schwarz/Mann ^{125}I radioimmunoassay, and acid concentrations were determined by titration to pH 7.0 with 0.1 *N* NaOH using a Beckman pH meter.

1. Test meals. After a 1-hr basal collection, dogs were fed 300 ml (approx. 0.25 lb) Wayne dried dog food (25% protein), which was consumed in less than 5 min. Collections of acid were made at 30-min intervals from 1 hr before the meal to 3 hr after. Venous blood samples (5 ml) for serum gastrin determination were drawn at −45, −15, 0, 15, 45, 60, 90, 120, and 180 min.

2. Insulin test. After a 1-hr basal collection, dogs were given 0.2 U/kg of insulin intravenously as a bolus. Gastric juice was collected in 15-min periods for 150 min. Venous blood samples for serum gastrin determination were drawn at −45, −15, 0, 15, 30, 45, 60, 90, 120, and 150 min. The greatest amount of acid secreted during one of the 15-min periods was the peak acid output (PAO).

3. Betazole and pentagastrin dose response. After a 1-hr basal collection, each drug was administered intravenously by continuous infusion through a Harvard pump in graduated doses for 45 min at each dose. The gastric juice obtained in the first

15 min of each collection was discarded, and the remaining two 15-min collections were averaged. Dose schedules were:

Betazole: 0.1, 0.25, 0.5, 1.0, 2.5, 5.0, 7.5 mg/kg/hr

Pentagastrin: 0.1, 0.25, 0.5, 1.0, 2.0, 4.0, 8.0 μg/kg/hr

Maximum acid output (MAO) was determined by pharmacokinetic methods in conjunction with computerized curve fitting.

4. Gastric emptying. Dogs were given a meal of 150 ml $BaSO_4$ solution in half of a can of dog food. Cineradiograms of gastric peristalsis were initially made under fluoroscopy, and plain abdominal films were made hourly thereafter until the stomach was judged to be empty.

5. Statistical analysis. All errors are expressed as standard error of the mean. Significance levels (P values) were calculated using Student's t test for the standard error of the difference of two means. Maximal acid outputs in dose–response experiments were calculated by linear least squares curve fitting to the equation

$$1/\text{acid output} = K_d/\text{dose} + 1/\text{MAO},$$

where K_d is a constant determining the slope of the relationship and 1/MAO is the intercept. Correlation coefficients on all of these Lineweaver Burke plots showed good positive correlation ($r^2 > 0.7$).

RESULTS

Gastric Fistula Dogs

1. Insulin test. The average peak acid response to insulin was 5.42 ± 0.46 meq/15 min for five GF dogs. After HSV in two GF dogs, there was a significant lowering of PAO to 3.32 ± 0.99 meq/15 min ($P < 0.06$). Subsequent CANL in these two dogs resulted in no further change in response to insulin (3.54 ± 0.52 meq/15 min). In three GF dogs, initial CANL caused a slight but insignificant increase in response to insulin over control to 7.30 ± 1.04 meq/15 min ($P > 0.09$). Subsequent HSV significantly reduced PAO below control (2.27 ± 0.74 meq/15 min, $P < 0.001$) (Fig. 2).

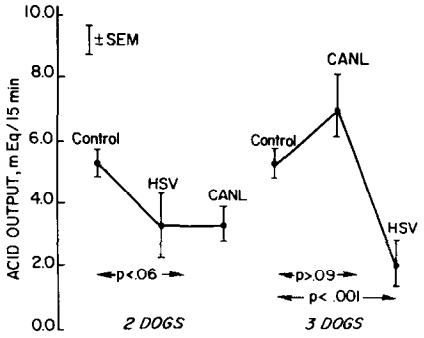

FIG. 2. Acid secretion in meq/15 min of gastric fistula dogs in response to 0.2 U/kg insulin at various operative stages.

2. Betazole and pentagastrin dose response. All GF dogs were tested for response to serial doses of pentagastrin and betazole. MAO was determined as maximal secretory rate by computer curve fitting techniques. Dogs with initial HSV showed no significant change from control with either betazole (MAO = 9.57 ± 0.98 → 8.21 ± 0.26 meq/15 min, $P > 0.15$) or pentagastrin (MAO = 7.05 ± 0.93 → 8.65 ± 1.67 meq/15 min, $P > 0.40$). Subsequent CANL resulted in no further change in MAO response to betazole (7.09 ± 1.12 meq/15 min, $P > 0.13$) or pentagastrin (7.56 ± 0.01 meq/15 min, $P > 0.6$). In GF dogs receiving CANL initially, responses to betazole (9.57 ± 0.98 → 10.2 ± 2.15 meq/15 min, $P > 0.8$) and pentagastrin (7.05 ± 0.93 → 6.60 ± 0.84 meq/15 min, $P > 0.6$) were essentially unchanged. Subsequent HSV did cause some decrease in response to both betazole (6.53 ± 0.92 meq/15 min, $P < 0.1$ and $P > 0.05$) and pentagastrin (4.60 ± 0.26 meq/15 min, $P < 0.05$) (Figs. 3 and 4).

3. Gastric emptying. The gastric emptying of all five fistula dogs was studied at each operative stage. Emptying times in all cases were between 3 and 5 hr as judged by hourly plain films, and the emptying time

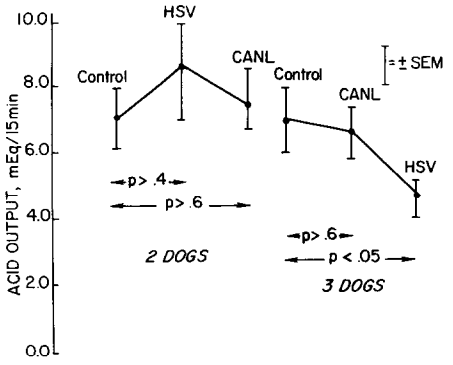

FIG. 3. Calculated maximal acid output in meq/15 min of gastric fistula dogs in response to pentagastrin at various operative stages.

for any given dog was unchanged by either HSV or CANL except for one dog, whose emptying time exceeded 5 hr following HSV. Cineradiograms showed coordinated obvious peristaltic waves traversing the entire antrum and lower fundus in all dogs in the control stage and remained unchanged throughout all operative stages except for the one dog following HSV in which only minimal fine uncoordinated peristaltic waves were seen.

Heidenhain Pouch Dogs

1. Betazole and pentagastrin dose response. Acid output of four HP dogs was measured in response to graduated doses of betazole and pentagastrin. Maximal pouch output (A_{max}) was determined by computer curve fitting. Individual values of A_{max} were dependent on pouch size, but A_{max} in response to pentagastrin or betazole was found to be comparable, and values of A_{max} were unchanged by CANL (Table 1).

2. Test meal. The maximal rise in acid secretion above basal was determined for each pouch dog. These values were normalized with respect to pouch size by dividing acid output in response to a meal by the pentagastrin A_{max} calculated from above. This normalized acid response to a meal did not change significantly following CANL ($0.385 \pm 0.078 \rightarrow 0.392 \pm 0.083$, $P > 0.92$).

Serum Gastrin

Basal serum gastrins in four pouch dogs were not changed significantly by CANL ($73.1 \pm 7.9 \rightarrow 59.2 \pm 6.4$ pg/ml, $P > 0.15$). After CANL alone, four normal dogs without a pouch also showed no significant change in basal serum gastrin ($81.2 \pm 4.9 \rightarrow 72.3 \pm 2.1$ pg/ml, $P > 0.13$). Maximum rise above basal serum gastrin in response to a test meal was also measured, this peak usually occurring between 45 min and 1 hr after the meal. The serum gastrin values were significantly elevated by the test meal in all cases, but the degree of elevation was not altered by the CANL in either the Heidenhain pouch dogs ($47.7 \pm 2.54 \rightarrow 40.9 \pm 3.69$ pg/ml, $P > 0.13$) or in the normal dogs ($27.5 \pm 3.41 \rightarrow 33.8 \pm 4.47$ pg/ml, $P > 0.16$ (Fig. 5).

DISCUSSION

The functions of the vagus and the cholinergic mechanisms involved in gastrin release are still a matter of debate, and there are notable species differences between man and dog [6, 23, 27]. While several authors have reported increased basal serum gastrin and an increased response of

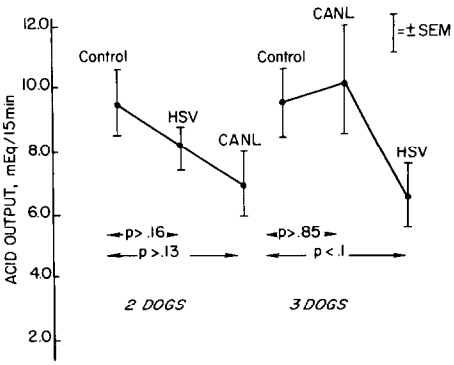

FIG. 4. Calculated maximal acid output in meq/15 min of gastric fistula dogs in response to betazole at various operative stages.

TABLE 1

MAXIMAL ACID OUTPUT OF HEIDENHAIN POUCHES IN RESPONSE TO PENTAGASTRIN AND BETAZOLE BEFORE AND AFTER CANL

Dog No.	Pentagastrin		Betazole	
	Control	CANL	Control	CANL
7233	3.3	2.8	3.3	2.7
6495	4.9	4.5	4.4	4.8
8815	4.4	3.9	Not measured	
8816	2.5	2.5	Not measured	

serum gastrin after vagotomies of all types [1, 4, 6, 15, 17, 26], others have noticed no difference between vagotomies, or no change in gastrin levels, or both [10, 12, 14, 24, 25, 27]. Atropine has been shown both to suppress early gastrin release after truncal vagotomy, and to enhance late release after the same operation [6]. Some authors contend that the vagus exerts both stimulatory and inhibitory influences on the antrum [6, 14, 17, 23, 24, 26]. The results presented here do not clarify these issues.

There are several possible reasons that CANL did not significantly alter gastrin responses to test meals. First, if vagal inhibitory effects are of greater importance than vagal stimulatory effects in the antrum [7, 27], submucosal denervation could remove the attenuating influence of the vagus, but this should lead to a rise in serum gastrin. It is also possible that following submucosal injection some important cholinergic feedback controls on gastrin release remain. If gastrin levels are mediated mainly by the submucosal plexus in response to changes in luminal contents, acidity, or pressure, then failure to denervate this plexus could leave serum gastrin responses virtually unchanged, since innervated gastrin cells might conceivably make up the deficit of gastrin caused by the denervation of other G cells.

It is also possible that the submucosal injections in our studies done without antral mapping might result in incomplete antroneurolysis, but one would expect a degree of change in serum gastrin response commensurate with the percentage of antrum denervated rather than an absence of significant change. Since failure to denervate small portions of the esophagus in HSV can result in relatively high levels of continued fundic secretion [9], small areas of innervated antrum might be sufficient to produce sizeable gastrin responses under feedback control. It is also feasible that intramural reflexes in areas not exposed to antroneurolysis could act by noncholinergic mechanisms on antral cells. The role of extraantral gastrin secretion is not well delineated, but may become more important in the presence of antral and/or fundic denervation [12, 27].

The effect of CANL on acid secretion in the gastric fistula dogs is not easily explained. CANL not only failed to reduce the acid response to betazole and pentagastrin following HSV, but as an isolated operation, may have even led to a slight increase in acid secretion after insulin. Radiologic studies showed that antral motility was unaltered by CANL. Dragstedt noted an increase in acid secretion by Heidenhain pouches after truncal vagotomy and phenol antroneurolysis, which he attributed to gastric stasis [7], but gastric empyting

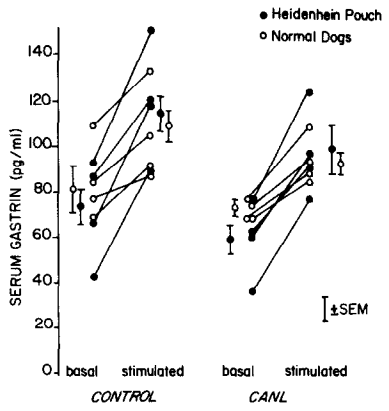

FIG. 5. Effect of CANL on basal and test meal-stimulated serum gastrin.

was shown to be normal following CANL in our experiments, so that gastric stasis is an unlikely explanation for our results.

In conclusion, we feel that the addition of CANL to HSV provides no significant advantage over the latter operation, while increasing its complexity. We therefore feel that improved surgical technique in HSV offers the best approach for decreasing the recurrence rate of this relatively low morbidity and mortality operation for peptic ulcer disease [9, 11, 13, 26].

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