# Effects of Anesthesia on Pancreatic Exocrine Secretion

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ANESTHETIC agents are commonly employed in the study of pancreatic secretion in experimental animals. Several authors have noted conflicting results under these circumstances and have remarked on the possible role of the anesthetic agent in their production. During studies involving perfusion of the pancreatic duct system [16] we found that basal secretion was markedly suppressed, and that the individual responses of animals to the same dose of secretin varied when the animals were anesthetized with sodium pentobarbital. The present study was designed to analyze in detail the effects of sodium pentobarbital and chloralose-urethane anesthesia on the pancreatic secretory response to secretin and pancreozymin.

## Methods

Fourteen mongrel dogs weighing between 16 and 21 Kg. were utilized. A Thomas cannula [15] was placed in the duodenum opposite the major pancreatic duct, after preliminary ligation of the accessory duct. A nylon coated stainless steel gastric cannula was placed in the most dependent part of the stomach to divert gastric secretion during subsequent experiments. Three animals, in addition, had truncal vagotomies added.

The animals were first studied at least 2 weeks following operation and were deprived of food but not water for 18 hours prior to each observation. Animals were studied no more than twice a week, and never on consecutive days. A continuous intravenous infusion of 0.15M sodium chloride was administered throughout each test at a rate of 50 ml./hr. The main pancreatic duct was cannulated under direct vision; the glass cannula was maintained in place by the adapter described by Rudick and Dreiling.[11] Pancreatic secretion was collected (a) under basal conditions in the unstimulated state, (b) in response to a submaximal dose of secretin (Vitrum)—1 u./Kg., (c) in response to a maximal dose of secretin—5 u./Kg., and (d) in response to 0.2 u./Kg. secretin + 1 u./Kg. pancreozymin (Cecekin, Vitrum). The secretin and pancreozymin used in these studies were all from the same batch. The gastric cannula was kept open during all observations to divert gastric acid secretion and prevent the release of endogenous secretin by acid contamination of the duodenal mucosa.

Repeated tests were performed on each animal to determine reproductibility. On each experimental day at least one test was carried out with the animal in the con-

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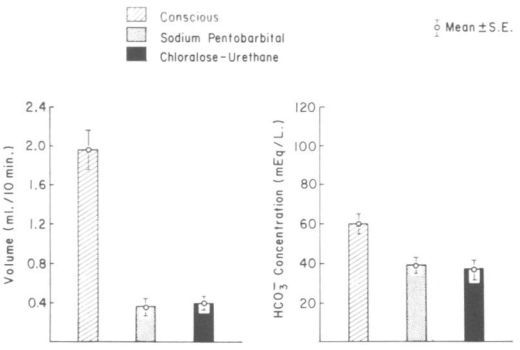


FIG. 1. Effects of sodium pentobarbital and chloralose-urethane anesthesia on basal secretion.

scious state. The animal was anesthetized with either sodium pentobarbital (30 mg./Kg. I.V.) or chloralose-urethane (1:10 w./w.) 80 mg./Kg. I.V. When the animal had reached a stable level of anesthesia, basal secretion was collected and the response to the various stimulants studied. At least one hour was allowed to elapse between successive injections, so that any altered response would not be due to a refractory gland.

In each experiment, pancreatic secretion was collected under oil in 10-minute periods and analyzed individually for volume, bicarbonate, chloride and amylase concentration. Bicarbonate and chloride were measured with a Technicon Autoanalyzer and amylase concentration by a modified Somogyi method. Statistical significance was determined by the Student's "t" test.[3]

## Results

**Basal Secretion.** Both sodium pentobarbital and chloralose-urethane caused marked depressions in volume response (Fig. 1). Basal secretion was reduced by 80% ($p < 0.01$). Concomitant with the decreased volume response was a reduction in bicarbonate concentration from 60 mEq./l. to 40 mEq./l.

**Secretin Stimulation** (Table 1). Volume responses to submaximal doses of secretin (1 u./Kg.) were reduced by 21% under barbiturate and 26% under chloralose-urethane anesthesia ($p < 0.05$). Responses to maximal doses of secretin (5 u./Kg.) were similarly reduced—34% under barbiturate and 21% under chloralose-urethane anesthesia ($p < 0.05$). In none of the experiments was the bicarbonate concentration significantly reduced. Volume responses are expressed as ml./20 min., while $HCO_3$ concentration is the mean result for the first 20 minutes following injection.

**Reproducibility.** The reproducibility of the volume response to 1 u./Kg. is illustrated in experiments on one dog in Figure 2. A highly reproducible response was seen in the conscious state (coefficient of variation 10%), whereas responses under both

TABLE 1. *Effects of Sodium Pentobarbital and Chloralose-urethane on Volume and Bicarbonate Responses to Submaximal and Maximal doses of Secretin*

| | $n$ | Volume (ml./20 min.) | $HCO_3$—Concentration (mEq./l.) |
|---|---|---|---|
| Secretin 1 u./Kg. | | | |
| Conscious | 34 | 31.2 ± 2.9 | 137 ± 5.8 |
| Sodium Pentobarbital | 26 | 24.5 ± 4.3* | 141 ± 6.2 |
| Chloralose-urethane | 16 | 23.1 ± 3.8* | 139 ± 6.5 |
| Secretin 5 u./Kg. | | | |
| Conscious | 18 | 35.6 ± 3.2 | 136 ± 6.1 |
| Sodium Pentobarbital | 12 | 23.6 ± 4.0* | 135 ± 5.9 |
| Chloralose-urethane | 10 | 28.0 ± 7.2* | 137 ± 7.2 |

$n$ = Number of observations.
* = $p < 0.05$.

forms of anesthesia were not nearly as reproducible, as is evidenced by the wide scatter of results. Coefficient of variation for the experiment illustrated was 27% for sodium pentobarbital and 53% for chloralose-urethane.

**Enzyme Response** (Table 2). Enzyme concentrations and output in basal samples were not analyzed because volumes obtained were frequently too small to allow accurate amylase determinations. In both experiments with secretin alone and with secretin + pancreozymin there were marked reductions in amylase concentrations with sodium pentobarbital ($p < 0.01$). Although there was a definite reduction in the amylase output during chloralose-urethane anesthesia, there was only a slight reduction in amylase concentration ($p > 0.2$).

**Effects of Vagotomy.** Three dogs subjected to vagotomy responded somewhat differently to the effects of anesthesia. Basal secretion in the conscious state and was only half that of the non-vagotomized animals (Table 3), although they were of similar weights. Both sodium pentobarbital and chloralose-urethane reduced basal secretion, but did so to a lesser extent than in the first group of animals. Bicarbonate concentration was already at a lower level with animals in the conscious state, and was not further reduced by either anesthetic. In sharp contrast to the non-vagotomized animals, the responses to maximal doses of secretin were unaffected by anesthesia. However responses in these animals in the conscious state were 30% lower than in the first group. Only sodium pentobarbital reduced enzyme responses to secretin and pancreozymin by 21% ($p > 0.2$).

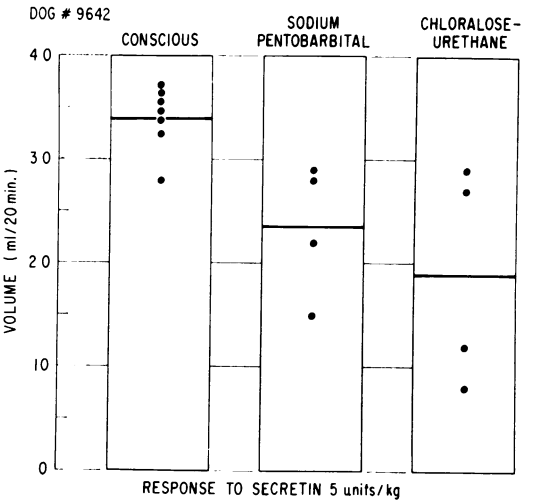


FIG. 2. Individual responses in one dog to 5 u./Kg. secretin. Each point refers to the result in an individual test while the bar refers to the mean.

**Relationship of Bicarbonate Concentration to Rate of Secretion.** Bicarbonate concentrations in all experiments were plotted against rate of flow; the typical hyperbolic relationship between bicarbonate concen-

TABLE 2. *Effects of Anesthetic Agents on Enzyme Concentration and Output in Response to Secretin Alone and with Pancreozymin*

| | *n* | Amylase Concentration (units/ml.) | Amylase Output (units/20 min.) |
|---|---|---|---|
| Secretin 1 u./Kg. | | | |
| Conscious | 34 | 8.0 ± 1.4 | 236 ± 38* |
| Sodium pentobarbital | 26 | 4.2 ± 1.2* | 102 ± 26* |
| Chloralose-urethane | 16 | 5.3 ± 1.4 | 118 ± 29* |
| Secretin 0.2 u./Kg. with Pancreozymin 1 u./Kg. | | | |
| Conscious | 22 | 15.6 ± 3.1 | 309 ± 32 |
| Sodium pentobarbital | 14 | 8.2 ± 2.0* | 129 ± 21* |
| Chloralose-urethane | 10 | 12.0 ± 3.6 | 219 ± 26 |

*n* = Number of observations.
* = $p < 0.01$.

TABLE 3. *Effects of Anesthesia on Volume, Bicarbonate and Enzyme Responses in Three Vagotomized Animals*

| | Conscious | Sodium Pentobarbital | Chloralose-urethane |
|---|---|---|---|
| Basal | | | |
| Volume (ml./10 min.) | 1.0 ± 0.2 | 0.4 ± 0.1 | 0.5 ± 0.2 |
| $HCO_3^-$ (mEq./l.) | 38.0 ± 3.6 | 30.0 ± 3.0 | 34.0 ± 3.2 |
| Secretin 5 u./Kg. | | | |
| Volume (ml./20 min.) | 23.1 ± 2.1 | 20.9 ± 2.3 | 22.4 ± 1.8 |
| $HCO_3^-$ (mEq./l.) | 132.0 ± 6.4 | 136.0 ± 5.8 | 137.0 ± 8.2 |
| Secretin + pancreozymin | | | |
| Amylase output (units/20 min.) | 185 ± 34 | 146 ± 32 | 178 ± 36 |

tration and flow rate was obtained (Fig. 3). The only experiments in which reductions in bicarbonate concentration occurred were those carried out in the unstimulated state. Analysis of these experiments revealed that the reduction of bicarbonate concentration was at all times proportional to reduction in flow. In the briskly secreting gland, reduction in bicarbonate concentration did not follow reduction in flow, since decrease in flow occurred at the horizontal part of the asymptote.

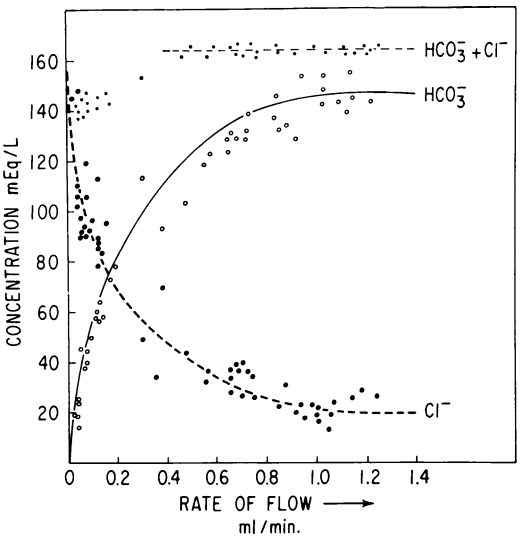


FIG. 3. Bicarbonate and chloride concentration plotted as a function of rate of flow. In the actively secreting gland, the sum of the two anions is always isotonic.

## Discussion

This study, which is summarized in Figure 4, demonstrates that anesthetic agents depress the pancreatic secretory response to exogenous secretin and pancreozymin. The pattern of depression is similar to the altered gastric secretory response to exogenous secretagogues found by several investigators.[10, 14] In a study on the influence of anesthesia on the pancreas, Friedman and Abromovage [4] reported that anesthetic agents reduced the pancreatic response to endogenous but not exogenous secretin. Possibly the less pure preparation of secretin used by these investigators may have masked these effects.

The marked depressive effects of anesthesia in non-vagotomized and lesser effects in vagotomized animals suggest that these effects are largely but not completely due to parasympatholytic effects of anesthesia. Vagotomy and atropine administration have been shown to diminish daily output of pancreatic juice (volume and enzymes)[5] and to decrease the pancreatic response to secretin.[9] However, chloralose-urethane is not generally regarded as having vagolytic effects.

Reduced responses may result from reduction in visceral blood flow, which could reduce glandular activity and its responsiveness to stimulation. This has been demonstrated for the stomach [6, 13] and may also be true for the pancreas, in which a rela-

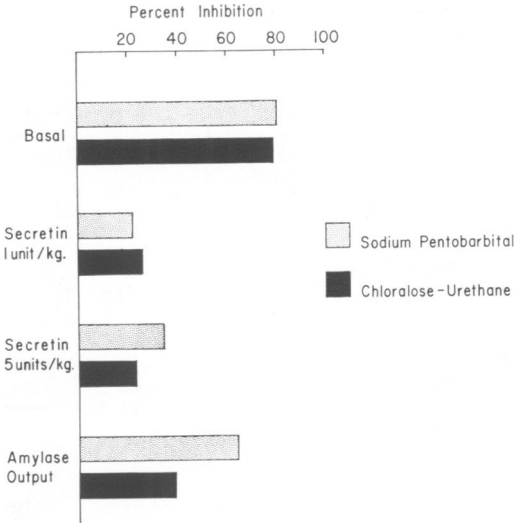


FIG. 4. Summary of depressant effects of anesthetic agents or pancreatic secretion in non-vagotomized animals. Results are expressed as mean per cent inhibition.

tionship between secretion and blood flow has been established.[2, 8] In the stomach, sodium pentobarbitone [12] depresses gastric blood flow and acid secretion and a similar mechanism may operate in the pancreas.

A possible mechanism is suggested by the study of Kitahara [7] who found that barbiturates reduce both acid secretion and oxygen consumption in isolated gastric mucosa. He postulated that this was due to inhibition of oxidative phosphorylation.[1] Some such direct effect on the pancreatic acini may be possible, but it is unlikely that anesthetics acted as metabolic inhibitors of acini in the doses used.

Although the responses to one and five units of secretin were reduced it is possible that calculated maximal secretory responses were unaltered. This means that under anesthesia the gland may be caused to secrete a volume equal to its maximum in the conscious state but that a higher dose of secretin is required.

In view of the frequency with which anesthesia is used in the study of pancreatic secretion, it is as well to be aware of the reduced and variable responses attendant upon the use of these agents. These effects may account for some discordance in physiologic observations and discrepancies in biological assays of secretin and pancreozymin recorded by different investigators utilizing anesthetic agents.

## Summary

The effects of two anesthetic agents, sodium pentobarbital and chloralose-urethane, were studied on pancreatic exocrine function. Both agents depressed basal secretion and the responses to submaximal and maximal doses of secretin. Volume and enzyme concentration were reduced in all experiments, but bicarbonate concentration was only reduced in the unstimulated experiments. Since this depressant effect was less evident in vagotomized animals, it suggests that it may largely result from parasympatholytic effects of the anesthetic agents, although other factors may also be contributory. The depressant effect should be borne in mind when interpreting studies on pancreatic function conducted under anesthesia.

## Acknowledgments

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## ERRATUM

In Shingleton, W. W.: Perfusion Chemotherapy for Recurrent Melanoma of Extremity: A Progress Report, Ann. Surg., 169:973, 1969, the name of *Dr. Herman A. Freckman* appeared incorrectly in Dr. Malcolm D. Thompson's discussion of the report.