Regional Variations in Responses of Rat GI Tract to Local Anesthetics

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Abstract □ The influence of four local anesthetics (procaine, tetracaine, lidocaine, and oxethazaine) upon acetylcholine-induced contraction of isolated segments of the rat GI tract was studied. The local anesthetics did not block the response of the stomach or colon to acetylcholine, but a reduction of the acetylcholine response of the duodenum similar to that seen with procaine was more pronounced with oxethazaine. Definite evidence was found which points to an anatomically defined specificity of the small intestinal motor effect of lidocaine in the rat.

Keyphrases □ Anesthetics, local—effect on acetylcholine-induced contraction of isolated rat GI tract segments □ GI motor activity—effect of local anesthetics on acetylcholine-induced contraction of isolated rat GI tract segments □ Acetylcholine contractions—effect of local anesthetics, rat GI tract

A number of studies have appeared on the effects of general anesthetic agents on various GI functions, but fewer studies have been reported regarding the action of local anesthetics on the muscular activity of the GI tract (1–5). In addition, those studies were only concerned with the motor activity of the small intestine, while the stomach and colon appear to have been neglected.

Therefore, the purposes of this study were twofold: (*a*) to determine the effect of directly applied local anesthetics to portions of the GI tract other than the small intestine, and (*b*) to determine the effects produced by prior direct administration of local anesthetics upon the cholinergic motor activity of the bowel.

EXPERIMENTAL

Methods—The classical tissue bath technique was selected as the most convenient to give the information sought. These experiments were performed on male Sprague-Dawley rats, with an average weight of 120 g. Each animal was fasted overnight and presented with laboratory chow[1] 15 min. prior to sacrifice. This procedure was shown to give a better isolated intestinal preparation (6).

The animals were sacrificed by cervical dislocation, followed quickly by the removal of 2–3-cm. segments of the duodenum, jejunum, ileum, and descending colon. The isolated stomach fundus strip preparation was used. In this experimentation the term proximal duodenum refers to that segment *juxta* the pylorus situated between the pyloric ring and entrance of the common bile duct, and the term distal duodenum refers to that portion of duodenum 4–6 cm. from the pyloric valve.

The responses of fundal and small and large intestinal segments to test drugs were recorded isotonically using a kymograph. The particular segments were mounted in parallel in a 50-ml. bath with Tyrode's solution. The Tyrode solution was gassed with 95% oxygen and 5% carbon dioxide and maintained at 38 ± 1° by a large, thermostatically controlled water bath surrounding the tissue container. The pH of the solution varied between 7.4 and 7.6. Tyrode's solution of the following composition was used (%): NaCl, 0.8; KCl, 0.02; $CaCl_2$, 0.02; $MgCl_2$, 0.01; $NaHCO_3$, 0.1; NaH_2PO_4, 0.005; and glucose, 0.1. Under these conditions, the spontaneous contractions were maximized and the viability of the preparations could be maintained for 4 hr.

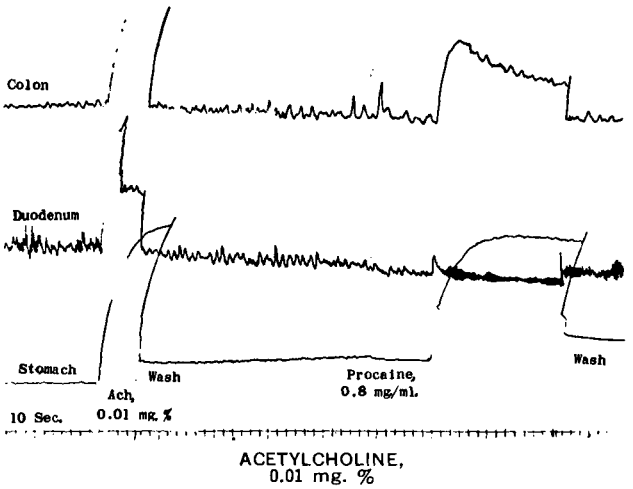

Figure 1—*Rat GI tract: record showing that prior administration of procaine inhibits the* in vitro *acetylcholine (Ach) response of the duodenum but not that of the stomach or colon.*

The segments were arranged so that longitudinal muscle contractions were recorded *via* a modified muscle lever. The free proximal portion of the bowel segment was attached to the muscle lever, with the distal end fixed to the bottom of the bath. The bowel segment was attached by thread in such a manner that it was completely submerged in Tyrode's solution, yet it was closed at each end so that the lumen was not bathed by the bath solution. This procedure ensured that the stimulus would be applied only to the serosal surface and that most of the force generated by muscular activity would be transmitted to the measuring system. No undue tension was applied to the segments during the mounting procedure. The only constant tension placed upon the segment was that of the lever which, in turn, was centered on its fulcrum and raised only until the attachment was tight enough to transfer the segment's movement to the recording stylus. The test segments were allowed to equilibrate for at least 10 min. prior to experimentation. Acclimation to the muscle bath environment was determined by consistency and/or rhythm of contractions. A synchronous timer recorded the time in 10-sec. intervals on the same tracing.

Materials—The following drugs were used: procaine hydrochloride[2], tetracaine hydrochloride[3], lidocaine hydrochloride[4], oxethazaine hydrochloride[5], acetylcholine chloride, and atropine sulfate[6]. The drug dose is specified as the final concentration of active base present in the tissue bath. Bowel segments were exposed to the action of the local anesthetics for 2 min. unless indicated otherwise on the record. Repeated trials were made with each drug in varying sequences of application on bowel segments of 46 different rats. These procedures were employed to determine if tachyphylaxis would be produced by any agent or if the nature of the response produced depended on the past history of experimental drug exposure.

[1] Purina.

[2] Abbott.
[3] Amethocaine hydrochloride (Harvey).
[4] Xylocaine hydrochloride (Astra).
[5] Wyeth.
[6] Sigma.

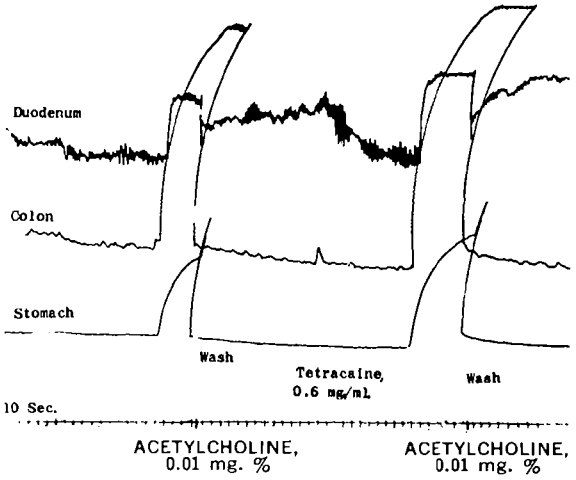

Figure 2—*Rat GI tract: record showing the failure of tetracaine to block the acetylcholine response of the excised stomach, duodenum, and colon.*

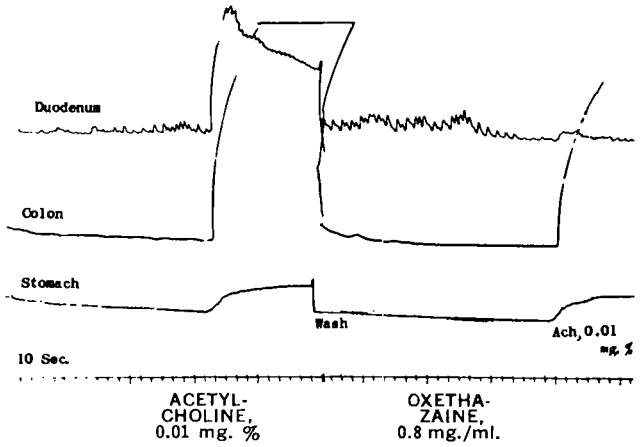

Figure 4—*Rat GI tract: record showing that prior administration of a low dose of oxethazaine inhibits the* in vitro *acetylcholine (Ach) response of the duodenum but not that of the stomach or colon.*

RESULTS AND DISCUSSION

Gastric Motility—Single muscle segments, taken from the stomachs of 15 rats, showed no spontaneous motor activities. Upon treatment with fixed doses of acetylcholine, these fundal segments exhibited tonic contractions of high magnitude. Gastric motility was found to be unchanged by the topical action of the anesthetics procaine, tetracaine, lidocaine, and oxethazaine. None of the anesthetic agents used inhibited the effect of repeated administration of acetylcholine on the stomach. The results are shown in Figs. 1–5.

Small Intestinal Motility—In all cases, small intestinal segments exhibited spontaneous motility when suspended in Tyrode's solution. In all nine trials of the local anesthetic oxethazaine, there was some relaxation in the tone of the longitudinal muscle and a reduction of the amplitude of the spontaneous contractions. From Figs. 4 and 5, it may be clearly seen that oxethazaine practically abolished spontaneous duodenal activity. Lidocaine in some instances also had a depressing effect on spontaneous small bowel contractions (Figs. 3 and 6). In sharp contrast, the effect of tetracaine in nine trials was to bring about a slightly increased state of contractility of the duodenum (Fig. 2).

Addition of procaine to the excised duodenum in six trials was without influence (Fig. 1). However, as shown in Fig. 1, procaine did depress the small intestine's response to acetylcholine. Tetracaine was ineffective in blocking the duodenal response to acetylcholine (Fig. 2). A reduction of the acetylcholine response of the duodenum similar to that seen with procaine was more pronounced with oxethazaine (Fig. 4). The extent of the reduction in contractility of the duodenum depended on the concentration of the oxethazaine in the bath becoming more pronounced with increasing concentrations (Fig. 5). Although not depicted, during oxethazaine depression the smooth muscle was unable to contract as strongly as the untreated muscle even if acetylcholine was given in concentrations as great as 0.1 mg. %. After the local anesthetic had been washed out, the gut segment failed to regain its original sensitivity to acetylcholine when challenged repeatedly for at least 10 min.

When different segments of the rat small intestine were examined, lidocaine had opposite effects in different parts of the duodenum of the same animal. As illustrated in Figs. 6 and 7, the proximal portion of the duodenum exhibited a unanimous relaxation response in 40 trials to a fixed dose of lidocaine, whereas both the jejunum and ileum exhibited only a contractile response in all 16 cases, each to the same dose of the local anesthetic. In Fig. 8 the response of the distal duodenum to lidocaine is biphasic, the largest portion of this response being the relaxation event. The kymogram also reveals that the stimulatory effect produced by lidocaine upon the duodenal and ileal tissues could be completely blocked by prior administration of atropine. There was gradually decreasing sensitivity of this drug from the ileo-caecal valve upward. The stimulating effect of this drug was more pronounced in the distal part of the terminal ileum (Fig. 7).

Colonic Motility—A total of 16 colonic segments were tested, with at least three segments challenged by each agent. As a rule the colon showed rhythmic motility very shortly after it had been placed in position in the bath and attached to the recording lever (Figs. 1, 2, and 5), but occasionally it was necessary to wait up to 6 min. before a suitable control tracing could be obtained (Fig. 4). Regardless, the local anesthetics had minor and seemingly inconsistent effects on the spontaneous motor activities of the colon.

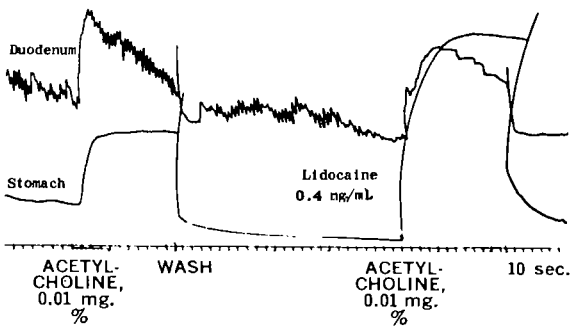

Figure 3—*Rat GI tract: record showing the failure of lidocaine to block the acetylcholine response of the excised stomach and duodenum.*

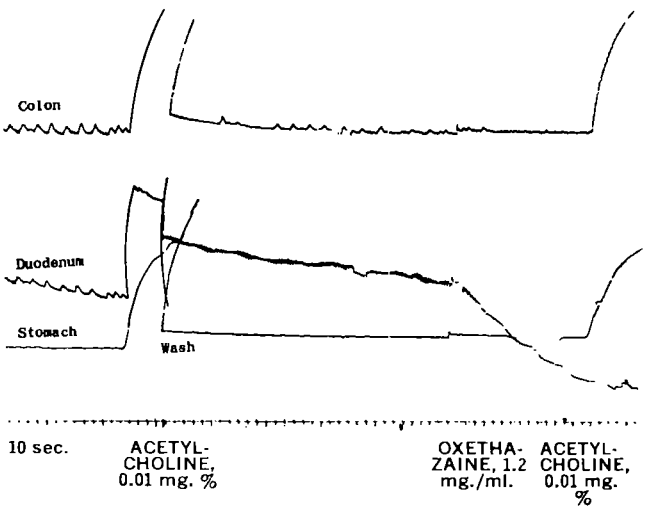

Figure 5—*Rat GI tract: record showing that prior administration of oxethazaine abolishes the* in vitro *acetylcholine response of the duodenum but not that of the stomach or colon.*

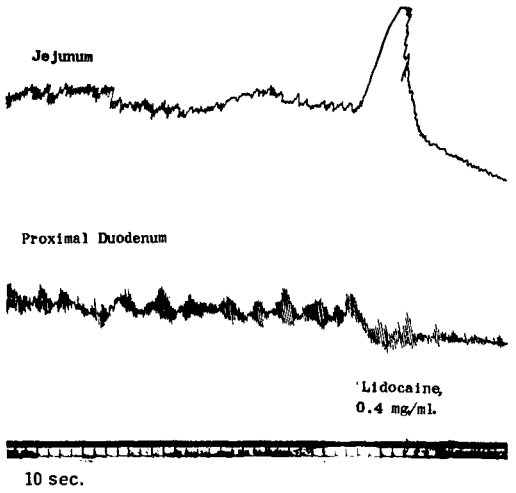

Figure 6—*Rat small intestine:* in vitro *responses of the jejunum and the proximal portion of the rat duodenum to lidocaine.*

None of the local anesthetics, including lidocaine, blocked the response of the colon to acetylcholine (Figs. 1, 2, 4, and 5).

It is significant that in the present work none of the local anesthetics employed had an excitatory or inhibitory effect on gastric or colonic motor activities. Furthermore, these failed to depress the response of the stomach or colon to acetylcholine, but procaine and oxethazaine did inhibit the response of the duodenum. No explanation can be given as to why gastric and colonic motility was never depressed other than suggest that inasmuch as the stomach and colon of the rat are much thicker tissues than the small intestine, it is possible that penetration of the tissues by the local anesthetics was incomplete. In the case of the colonic muscle strips, the results might have been different if the mucosal surfaces had also been exposed to the agents, although we know of no reason to suspect that this might actually be the case. The results obtained demonstrate that procaine and, to a greater extent, oxethazaine antagonized the stimulatory action of acetylcholine in the rat small intestine. The question whether the antagonistic effect of oxethazaine is due to a competitive inhibition or is related to a nonspecific action, as is known to be the case with procaine, has not been particularly studied.

The remaining results reported here demonstrate that when different parts of the small intestine were examined, inhibition by the local anesthetic lidocaine was found to occur regularly in the proximal duodenum while stimulation occurred in the jejunum and ileum, so lidocaine had opposite effects in different parts of the same gut. Lidocaine produced a prolonged inhibition of proximal duodenal motility and tone, whereas the more transient stimulatory effect of lidocaine on the distal duodenum, jejunum, and ileum could be blocked by atropine.

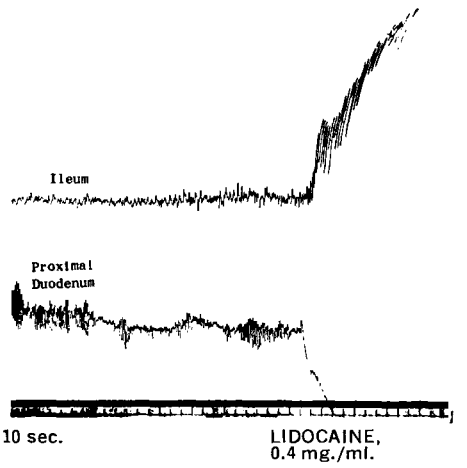

Figure 7—*Rat small intestine:* in vitro *responses of the terminal ileum and proximal portion of the rat duodenum to lidocaine.*

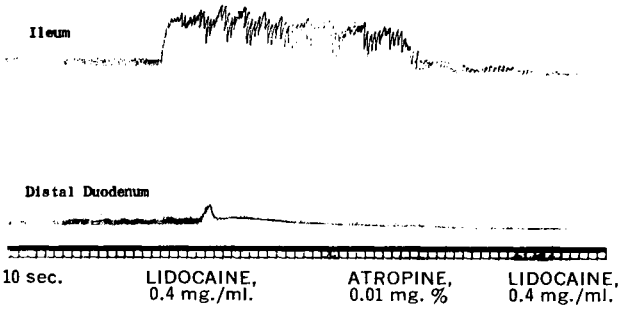

Figure 8—*Rat small intestine:* in vitro *responses of the ileum and distal portion of the rat duodenum to lidocaine and the abolition of these responses by atropine.*

At present, no widely accepted hypothesis has been advanced which accounts for this observed difference in the lidocaine response of proximal and distal segments of the rat small intestine, other than to suggest that the predominantly relaxation response of the proximal duodenum to lidocaine is related to the abundance of adrenergic innervation, which is more prominent in this region of the duodenum. The response of the rat intestine to lidocaine exhibited a decreasing relaxation event and an increasing contractile event with the increasing distance of the tissue from the regions of greatest adrenergic innervation.

The mechanism by which this relaxation event is mediated has not been clarified by this investigation. It is not possible to determine whether the relaxation response to lidocaine is the result of the release of endogenous catecholamine or of a direct action of this chemical on adrenergic receptors. On the other hand, it has been quite definitely established that the contractile events of the small intestine do appear to be mediated by acetylcholine, since the lidocaine-induced contractile responses of these segments were completely antagonized by atropine.

In summary, the important point to be noted from these results, apart from their general pharmacological significance, is that the variable response of the small intestine to lidocaine is an example of a caveat which must apply to pharmacological investigation in general: that a broad anatomic designation (*e.g.*, small intestine) does not always guarantee the reproducibility of results in response to a well-defined stimulus.

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