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Note

A computerized artificial stomach model to assess sodium alginate-induced pH gradient

J. Vatier *, C. Célice-Pingaud, R. Farinotti

INSERM., Département de Pharmacie Clinique, Faculté de Pharmacie, 92290 Châtenay Malabry et Biochimie B (Pr. Nunez), CHU Xavier Bichat, 46 Rue Henri Huchard, 75018, Paris, France

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Abstract

A computerized 'artificial stomach' model capable 1) of measuring the pH both in gastric contents, using a combined glass electrode, and at its surface, using a surface microelectrode, 2) of simulating the gastric emptying regulation in regard to the intragastric pH in physiological situation and 3) of controlling the position of the surface microelectrode in regard to gastric volume variations by means of a surface detector system, has been used to analyze the antacid activity and the pH gradient induced by both alginate-containing drugs, different in their carbonate composition. When added to 0.1 N HCl solution, both drugs developed a floating 'raft' at the surface supporting a pH gradient (close to 4 pH units) simultaneously with a moderate or weak antacid activity in gastric contents. Both studied drugs are capable of exerting a protective effect in gastro-esophageal reflux disease mainly by the induction of a pH gradient.

Keywords: Artificial stomach; pH gradient; Sodium alginate; Gastro-esophageal reflux

To assess in vitro the antacid capacity and the pH gradient induced by sodium alginate-containing drugs, we have previously developed a model of 'artificial stomach' capable of measuring simultaneously the pH both in gastric contents (GC), using a combined glass electrode, and at its surface, using a surface microelectrode (Vatier et al., 1990). To simulate the therapeutical conditions, the original model has been improved by developing a computerized 'artificial stomach' model capable of simulating the gastric emptying regulation in regard to the intragastric pH in physiological situation and of controlling the position of the microelectrode in regard to gastric volume variations by means of information given

* Corresponding author.

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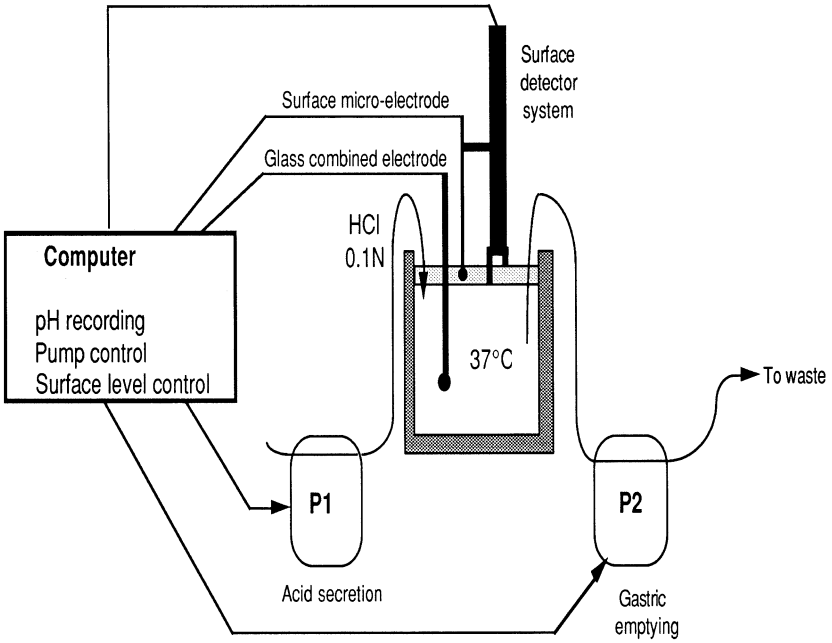

Fig. 1. Schematic representation of the computerized 'artificial stomach' model including a glass combined electrode immersed in the gastric contents and a surface microelectrode maintained at 5 mm below the surface by means of information given to the computer by a surface detector system.

by a surface detector system (Vatier et al., 1996a). This model has been used to study the pH variations in GC and at its surface after adding one therapeutical dose (10 ml) of two sodium alginate-containing drugs, different in their contents of antacid load.

Drug A: $CaCO_3$ 1.20 g—$NaHCO_3$ 0.30 g—$MgCO_3$ 0.14 g—Na alginate 0.30 g/10 ml (Rennie® alginate)

Drug B: $CaCO_3$ 0.16 g—$NaHCO_3$ 0.26 g—Na alginate 0.51 g/10 ml (Gaviscon®)

The computerized 'artificial stomach' model consisted of a glass beaker standing on a magnetic stirrer. At time t_0, it was filled with 200 ml 0.1 N HCl solution simulating an acid hypersecretion state. It received a constant flow of acid secretion consisting in 0.1 N HCl solution (3 ml/min) and emptied to the waste. Two electrodes were positioned, the first one, a combined glass electrode, in the GC and the second, a surface microelectrode, at 5 mm below the surface. The microcomputer controlled the output flow of the individual pumps which in turn controlled acid secretion (P_1) and emptying (P_2) flows. It received feedback from the surface sensors placed at the level of the surface of the GC and adjusted the position of the surface microelectrode permanently at 5 mm below the surface in spite of volume variations in the GC (Vatier et al., 1996b) (Fig. 1). The GC was kept at 37°C, using double walled beakers through which hot water circulates.

Assays were carried out to simulate the physiological gastric emptying regulation, i.e. gastric emptying speeds up as the pH rises and slows down as it falls. The values for emptying flow introduced in this program corresponded to those published in intragastric titration in response to liquid meal (Duval de Laguierce et al., 1986) and in antral acidification response in healthy volunteers (Merrouche et al., 1985).

Six assays were performed and the results were expressed as the mean $\pm$ S.D.

In these conditions, addition of both tested drugs to 200 ml of 0.1 N HCl solution exerted a moderate antacid effect and induced a floating 'raft' at the surface which supported a pH gradi-

ent between GC and its surface; maximum pH in GC: $A = 1.61 \pm 0.22$, $B = 1.29 \pm 0.11$ vs at the surface: $A = 6.28 \pm 0.61$, $B = 5.47 \pm 0.75$ ($P < 0.001$). After 75 min, it was observed a slight decrease of the pH gradient intensity with B evidencing a raft permeability to H^+ ions, while pH at the surface remained constant for 120 min with A; mean pH at the surface for 120 min $A = 5.70 \pm 0.20$, $B = 4.80 \pm 0.89$ (Fig. 2).

When preventing the formation of the floating 'raft' induced by A and B at the surface by a strong stirring, the pH gradient between GC and its surface was no more observed: the maximal pH is similar in the GC and at the surface (i.e. 5.45 ± 0.05 vs 5.45 ± 0.02 with A and 1.56 ± 0.02 vs 1.58 ± 0.03 with B), indicating that A developed a greater antacid capacity than B ($P < 0.001$).

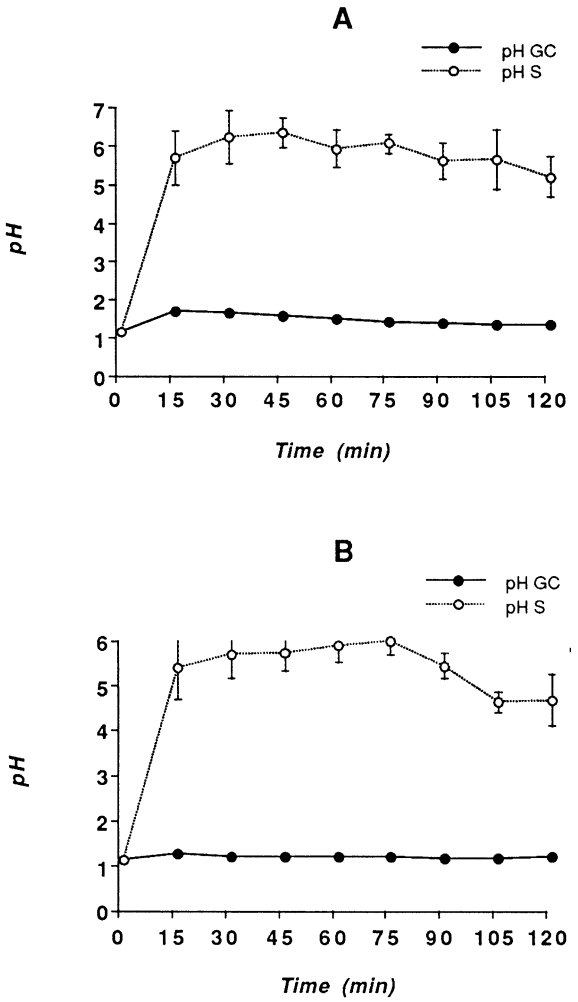

Fig. 2. Evolutions of pH in GC and at its surface for 120 min when 10 ml of A and B were added to 200 ml of 0.1 N HCl solution (●, Gastric contents pH; ○, Surface pH).

The computerized 'artificial stomach' model used in this study is an improvement of the original model (Vatier et al., 1990) since it is able 1) to simulate the physiologic gastric emptying flux in regard to intragastric pH, taking thus into account the incidence of the antacid activity and 2) to correctly evaluate pH gradient since the surface microelectrode is maintained continuously at the same position despite intragastric volume variations, contrary to the manual adjustment of this electrode resulting in artefactual pH variations. In these conditions, in pH 1.0 medium, B drug induced a pH gradient close to 4.0 pH units instead close to 2.0 pH units as shown in a previous study based on the manual adjustment of surface electrode position (Vatier et al., 1990). In addition, the GC is maintained at 37°C in these assays and the physiologic gastric emptying regulation is simulated, corresponding to in vivo situation.

The pH within GC depends on the ratio between the load and the nature of the antacid salts + the alkaline load consumed by the raft formation and the acid amount to which they were added. In the experimental conditions, studied drugs induced a pH-rise at 1.29 rapidly with B and at 1.61 slowly with A, difference related to the pK_a of CO_3^{2-} (pK_a close to ten) and of HCO_3^- (pK_a close to six).

Both alginate-containing drugs, added to 200 ml of 0.1 N HCl solution, developed a floating 'raft' at the surface which supported a pH gradient of the same intensity resulting in a perceptible modification of the surface close to 1–2 cm thick in the beakers. Inside this floating 'raft', when measuring pH with the surface electrode at different levels, it could be observed an increase of the pH from the lower to the higher part. We have deliberately chosen to place the surface microelectrode at 5 mm below the surface to record a mean pH within the raft, in the same conditions, for all assays. Progressively the floating 'raft' might become permeable to H^+ ions as shown with B

drug. This permeability is related to physical quality of the raft. When preventing the pH gradient formation by means of strong stirring, the pH values are similar in GC and the surface, more increased with *A* than with *B*. This result led to the hypothesis that the antacid load in alginate-containing drugs would be divided in two parts, the first one, with a weak intensity, at the GC level and the second, more important, into the floating 'raft'.

The studied drugs are thus adapted to the medical strategy in the treatment of the disorders due to gastro-esophageal reflux disease (GERD) which involves to decrease the total number of reflux episodes in 24 h period and the aggressive nature of the refluxate, preventing thus the development of erosive esophagitis. Although these drugs would decrease weakly the gastric acidity of the refluxate, they are capable of decreasing the total duration below pH 4 and the number of the reflux episodes as shown with alginate-containing drug *B* in infants and children (Evans et al., 1986; Buts et al., 1987; Vandenplas and Sacré-Smits, 1987; Leluyer et al., 1992), in patients suffering from GERD (Dudicourt et al., 1988) as well in healthy volunteers (Stoddard and Morgan, 1989). A multicentric study has shown that subjects treated with *B* drug were significantly more improved than those treated with a prokinetic drug and that the cost of this treatment is cheaper (Poynard et al., 1996). Indeed sodium alginate is known to act as an antireflux barrier when it forms a floating 'raft' on top of the gastric pool which might be particularly effective for the breakthrough symptoms occurring with postprandial upright activity during the day in these patients (Castell et al., 1992; Washington et al., 1992). Our study shows that *A* and *B* induce a strong pH gradient between GC and the surface for a long duration (>120 min). In addition the strength and cohesiveness of the floating 'raft' is probably able to prevent pepsin to cross to gastro-esophageal mucosa.

The computerized 'artificial stomach' model allows us to quantify the pH gradient intensity and to anticipate the therapeutical events. In the clinical situation of the gastro-esophageal reflux, these studied drugs seem to be efficient as protective drugs mainly by their ability to induce a pH gradient.

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