CLINICAL IMPLICATIONS OF BASIC RESEARCH

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Stomaching Drug Delivery

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Oral ingestion remains the preferred method of drug administration. Its disadvantages with regard to biologic agents reflect the fact that systemic bioavailability is influenced by the chemical properties of the drug and by the gastrointestinal physiological and pathologic features of the patient. Unfortunately, many candidate biologic agents are labile or cannot readily cross the gastrointestinal epithelium.

Oral delivery of therapeutic peptides, proteins, antibodies, and genetic medicines has been one of the most sought-after goals of the pharmaceutical industry for decades. There have been few successes. Nonetheless, three oral formulations that were based on combining peptides with permeation enhancers are in phase 3 clinical trials,[1] although their oral bioavailability is low and variable. It can be concluded that conventional oral formulation suits only a subset of macromolecules — those that are stable, are highly potent, and are cleared slowly. Investigators seeking to improve macromolecule delivery are therefore increasingly turning to drug–device combinations to allow progress beyond the incremental advances that have occurred over the past decade with traditional pharmaceutical formulations.[2]

Abramson et al.[3] recently described a prototype gastric device, dubbed a self-orienting millimeter-scale applicator (SOMA), which is designed to orient at the stomach wall, at which point an actuated needlelike attachment (called a millipost) incorporating the therapeutic entity penetrates and deposits the payload (that is, the millipost) across the mucosa for systemic distribution (Fig. 1). The study builds on the extensive bioengineering experience with gastroretentive gadgets. Several of these are already marketed for the delivery of small-molecule drugs, which, on release in the stomach, are subsequently absorbed in the upper small intestine.[4]

Abramson et al. drew inspiration from the shape of the shell of a self-righting tortoise. Once the SOMA is apposed to the stomach wall, having arrived at it by force of gravity or gastric pressure, actuation occurs by means of a fluid-induced dissolution process that deploys a spring, forcing the millipost to pierce the gastric mucosa, yet avoiding perforation of the underlying smooth muscle. Abramson et al. tested the device in three fasting pigs, using human insulin as a model active pharmaceutical agent. The large body of preclinical and clinical pharmacokinetic and pharmacodynamic data on insulin makes it a good choice for proof-of-principle studies. The SOMA devices, containing 0.3 mg of human insulin, were delivered directly to the stomachs of the pigs, avoiding the oropharyngeal and esophageal domains, although the apparatus is small enough to be easily swallowed in a capsule. The authors observed by means of endoscopy and radiography that the SOMA rapidly assumed the desired orientation against the gastric wall despite changes in posture, viscosity, and agitation of stomach contents. Although the milliposts, which are made by compressing insulin with poly(ethylene) oxide, dissolved within 60 minutes, the duration of device residency in the pigs' stomachs was highly varied — between 1 day and 7 days, in spite of normally effective gastric emptying. The monogastric pig stomach is similar but not identical to that of the human with regard to size, structure, physiological variables, and function.

After placement of the SOMAs, the authors observed hypoglycemia-inducing reductions in plasma glucose levels over a period of 30 minutes to 2 hours, accompanied by a transient rise

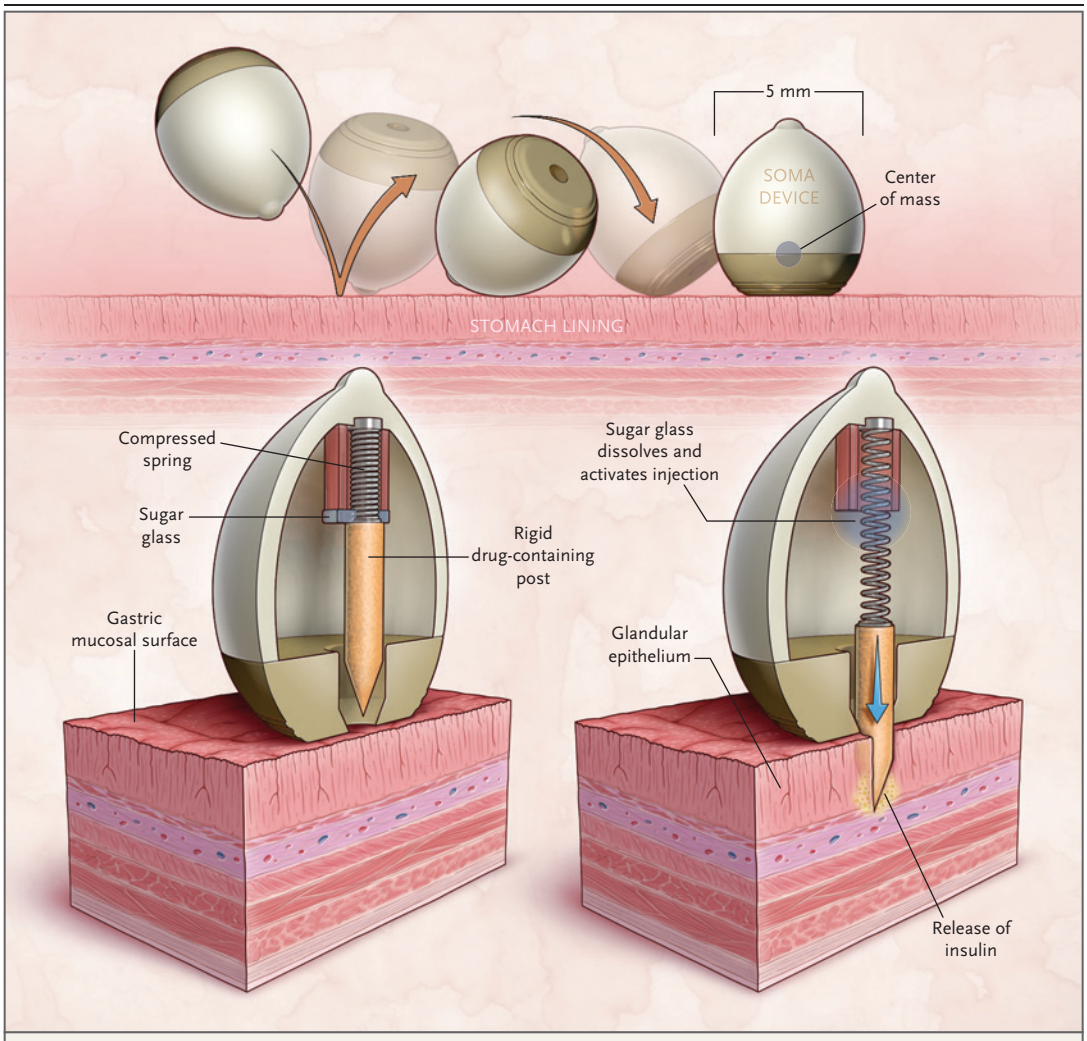

Figure 1. Breaching the Gastric Mucosa.

Abramson and colleagues[3] recently reported a preclinical test of a self-orienting millimeter-scale applicator (SOMA), which was designed to land on the gastric mucosal surface under the force of gravity and to orient in apposition to the plane of the tissue. A timed spring-release trigger fires to pierce the gastric mucosa with a rigid, drug-containing post (called a millipost). The device is attached to the gastric mucosa, which is pierced to a depth of several millimeters to breach the glandular epithelium to the depth of approximately the muscularis mucosae. The drug diffuses into systemic blood. After the millipost dissolves, the SOMA moves through the gastrointestinal tract and may be recovered in the feces.

in the plasma level of human insulin. Studies in rats and pigs showed that placement of the devices was not accompanied by changes in feeding and stooling patterns and that the devices could be recovered in the feces. The investigators also tested the devices fitted with 3-mm needles, instead of with milliposts of powdered insulin, to gauge potential adverse events on misfiring and observed none over the course of 9 days. The study therefore shows that the stomach is a potential site for systemic macromolecule delivery by physical means rather than by chemical permeation enhancement.

Some aspects of this study will need to be built on in future studies — notably, a focus on studies with delivery from an oral capsule in a large animal model rather than intragastric delivery, in which a greater degree of intrasubject

variation can be expected. In addition, it is unclear whether positioning the device by gravity is a better strategy than others, with respect to attachment to the intact wall of the stomach. The impalement process is vectorial and is presumably influenced by intragastric pressure, which is scalar. The toxicologic implications also need to be examined more closely. Scale-up and manufacturing of such devices are required to enable translation to clinical trials. Such efforts may be encouraged given the recent announcement of a successful safety study involving humans that used balloon-stimulated microneedles aimed at delivering biologic agents across the small intestine.[5] For now, we conclude that this study has leveraged both the gastroretentive device field and learnings from small intestinal device-based systems to achieve a proof of principle for the delivery of peptides in a large animal model.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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