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Medical devices made of substances in the management of patients with gastrointestinal diseases

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The gastrointestinal tract is the most frequently used way of access for any type of oral therapies and a preferential one for Medical Devices Made of Substances (MDMS) which can accomplish their therapeutic activities at three different levels:1) within the lumen, 2) on the epithelial barrier, and 3) systemically, after being absorbed. Many gastrointestinal disorders and diseases benefit of MDMSs to be used as add-on treatment to pharmacological agents, substitution of medicine that are either ineffective or causing unbearable side effects and in several conditions in which medical treatment is not available or cannot be utilized. The best clinical indication of MDMS is in patients with chronic gastrointestinal diseases caused by multifactorial factors that cannot be properly tackled by a medicinal product acting on a single receptor whereas a medical device made of complex or natural substances, devoid of receptor effect, can profitably and synergically act on several different pathogenetic mechanisms.

Introduction

Many gastrointestinal disorders and diseases benefit of medical device made of substances (MDMS) and their therapeutic use precedes since long time the recent official statements by governmental agencies defining them for the different mechanism of action from the medicinal products, which is, as explained in the article by Racchi and Govoni published in this issue of the Journal, non- pharmacological, non- metabolic and non-immunological. It is well known the historical use of antacids and osmotic laxatives that exert their action within the gastrointestinal lumen outside of, and without any interaction with, the organism. The digestive tract, not differently from the skin and the respiratory system, has a fundamental function as a barrier to separate the organism from the outside environment of the lumen and has offered so far a great opportunity for medical products to exert beneficial effects by acting either within the lumen and/or on the epithelial barrier being, thus, devoid of any pharmacological, metabolic, and immunological effect on the organism. From now on, however, the recent European Rule 21 2017/745/EC recognizes that MDMS can act also following systemic administration and absorption (1) to include those complex products that exert multiple reactions with the human body not acting at a single target/receptor level. Hence, in addition to the luminal area and vast epithelial barrier, the gastrointestinal tract offers also the great absorptive capability to handle MDMS. In clinical prac-

tice the main indications of MDMS are for add-on treatment to pharmacological agents, substitution of medicine that are either ineffective or causing unbearable side effects and in several conditions in which medical treatment is not available or cannot be utilized. One or more of the above-mentioned limitations of the medical agents often occur in the treatment of chronic or recurrent diseases that, being chronic by definition, defy a ultimate resolution. In addition, chronic diseases usually have multifactorial pathogenetic factors that cannot be tackled alone by a medicine that, by acting on a single receptor, would limit its effect on one of the many pathogenetic factors. Differently from a medicine, a MDMS does not have a receptor effect and, moreover, can be made of complex substances which can synergically act on several different pathogenetic mechanisms. Probably the best example of a chronic gastroenterological condition in which MDMSs find a useful indication is for heartburn and dyspeptic symptoms. Despite the widely accepted medical treatment based on gastric acid reduction with antacids, H_2 receptor antagonist and PPI, the response rate. In these conditions is far from satisfactory. We now know that the pathophysiologic mechanism of heartburn is much more complex than gastroesophageal acid reflux and other factors such as the non-acid reflux, the wide intercellular spaces of the esophageal epithelium leading to a reflux-induced immune and antioxidant sensibilization of the esophageal peripheral nerve fibers (2-3) are not responsive to an acid suppressive treatment. Thirty percent of gastroesophageal reflux patients with endoscopic evidence of esophagitis do not respond to PPI, and in those who respond and obtain mucosal healing with initial PPI treatment, long-term PPI treatment will progressively loose the benefit of the symptomatic response and the mucosal healing (4). Forty per cent of non-erosive reflux disease (NERD) patients and all functional heartburn patients do not respond to PPI treatment (5). PPI cannot be used during pregnancy and are strongly discouraged in infancy. Side effects of short-term PPI treatment are infrequent and usually well tolerated, however in a few patient unbearable side effects force to stop the treatment. In patients with specific diseases such as decompensated cirrhosis or osteoporosis, long-term treatment with PPI is discouraged and in many of these cases it cannot be used (6-7). Even less effective are the medicinal products on the symptoms of functional dyspepsia for which PPI are the first indication according to the actual international guidelines although they offer clinical benefit in no more than 35% of the patients (8). This explains why products not acting with pharmacological, metabolic and immunological means have been used historically in all these conditions of heartburn and dyspeptic symptoms. The first attempts were made, with limited benefit, using antacid substances by simply buffering the gastric acid secretion; more recently, in the attempt to tackle more efficiently one or more pathophysiological factors of heartburn and dyspeptic symptoms, medical devices were developed to oppose the reflux of gastric contents into the esophagus or to reinforce the esophageal and gastric epithelial barrier. Nowadays, the possibility for a medical device to be made from natural substances, and hence with more components acting in synergy, enables to create a complex compound having, at the same time, an epithelial barrier protection as well as antacid and antioxidant activities. As a matter of fact, such medical devices find their clinical application as add-on treatment to not fully effective PPI therapy, in patients not responding to PPI or with unbearable PPI side effects, during pregnancy, in childhood and whenever PPI are contraindicated or not tolerated. Being widely available, a practical use of a medical device is also possible for mild or infrequent episodes of heartburn and dyspeptic symptoms in everyday life. Another gastrointestinal chronic condition with limited therapeutic response is the Irritable Bowel Syndrome (IBS). IBS has different symptomatic expressions and, traditionally, the treatment is directed to the more bothering symptom, be either abdominal pain, or diarrhea or constipation (9). However, despite this approach is the most widely applied, it offers only a limited and temporary benefit for the main symptom, without improving or even aggravating the other disturbances of the syndrome. So, treating the pain with antispasmodics makes constipation worse, and, viceversa, a stimulant laxative for constipation can aggravate abdominal pain. In recent years, several molecules with specific receptor activity, such as guanylate cyclase-C agonist and $5HT_4$ agonist for IBS-Constipation, $5HT_3$-antagonist and opioid-receptor

agonist/antagonist for IBS-Diarrhea, have been developed but their limited efficacy and frequent, and sometimes unbearable, side-effects have limited their use as second-line therapy and in a minority of patients. The mutifactorial pathogenesis of IBS recognizes as the main mechanisms of the syndrome the increased permeability of the epithelial barrier and a low-grade mucosal inflammation. The luminal environment, with bacteria, viruses, fungi, food degradation products and many other antigens, is normally controlled by the epithelial barrier. Whenever barrier permeability increases, the stimulant luminal components activate the mucosal immune system and ROS and thus triggers the enteric nervous system, the neuro-muscular reflexes and enhances the sensitivity of the afferent nervous fibers leading to the clinical expression of pain and altered gut contractions and secretion. Likewise physical and psychological stress can, via nervous and humoral brain-gut connection, activate the mucosal immune system and increase epithelial barrier permeability The low grade inflammation increases the barrier permeability that, in turn, maintains the mucosal inflammation in a vicious cycle that may progressively lead to the severe symptomatic expression of the syndrome (10). In IBS, a complex MDMS made of natural substances can target the main pathophysiological factors aiming to reinforce the epithelial barrier and to have ant-inflammatory and antioxidant activities. Complex MDMS can likewise target multiple mechanisms in other functional intestinal disorders such as Functional Constipation and Functional Diarrhea, being efficient while avoiding the usual side effects of the habitual pharmacological armamentarium. In addition, the minimal side effects and the lack of receptor ligands make MDMSs the ideal products as add-on treatment in the therapeutic management of patients with inflammatory bowel disease who, despite inflammatory remission with antinflammatory drugs, may still present bowel dysfunction and abdominal pain. The minimal side effects and the lack of receptor ligands make likewise MDMS useful in patients with polypathology and polypharmacology as they may substitute, or be added to, some of the receptor targeting drugs.

In conclusion, the multiple physiological mechanisms that can be targeted by MDMS, and even more by complex MDMS made of natural substances, make these medical devices largely used in clinical practice in an ample spectrum of medical conditions. The luminal space and the epithelial barrier of the gastrointestinal tract are natural and amenable non-receptor targets for MDMS that find their main indications in a wide spectrum of chronic gastrointestinal disorders and diseases in which medicinal products exerting their mechanism of action by receptors ligands have limited therapeutic efficacy and are not devoid of relevant adverse effects.

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