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Editorial

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FUTURE TREATMENT OF PEPTIC ULCER: IS THERE ROOM FOR ANTI-INFECTIVE DRUGS?

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Several major Laboratories have recently given up their search for uncovering innovative antiulcer drugs despite the fact that none of the available drugs meet the ideal aims of therapy: to relieve pain, to heal the ulcers and to prevent the recurrences. Furthermore, no single antiulcer drug has proven effective in managing ulcer-related complications or ulcers associated with oncology and sclerotherapy treatment. Recent research suggests that the eradication of H. pylori infection is associated with decreased rate of duodenal ulcer recurrences, however, appropriate and convenient eradication therapy needs to be developed. Moreover, we must also continue to search for ideal drugs effective for the treatment of ulcers and their complications.

Key Words: *bismuth salts, histamine H_2 antagonists, misoprostol, omeprazole, prostaglandins, H. pylori, ulcer complications, ulcer recurrence.*

Therapeutic research approaches to the medical management of peptic ulcer disease had seen significant evolution during the past two decades. Although the precise etiology of peptic ulcer disease is still unknown, it is generally accepted that ulcers occur when the luminal aggressive factors overcome mucosal defense mechanisms. The aggressive factors include, but are not limited to, gastric acid, pepsinogen, bile salts and exogenous factors such as smoking and non-steroidal anti-inflammatory drugs (NSAIDs). The defensive factors include cell renewal and restitution, the gastric mucosal barrier with its mucus, bicarbonate, prostanoids and a rich mucosal blood flow. More

recently, several lines of evidence also indicate possible infectious basis in the etiology of this disease. Helicobacter pylori is a spiral-shaped bacterium that has recently been associated with antral gastritis and duodenal ulcer recurrences. H. pylori has been found in up to 100% of patients with peptic ulcer disease. However, some 25% of healthy subjects are infected by this bacteria, and 50% will become infected at the age of 50 years (1, 2). Yet very few of these healthy subjects ever develop an ulcer. This indicates that the H. pylori is probably another member of the human gut bacterial flora. Perhaps, under some mysterious conditions, this innocent bacteria become pathogenic.

During the past two decades, diverse types of drugs have become available for the medical management of peptic ulcer disease (3). The ideal aims of treatment of peptic ulcers are to relieve pain, heal the ulcer and delay or prevent ulcer recurrence. To date, no drug meets all goals of therapy. Drug treatment of peptic ulcers is targeted at either counteracting aggressive factors or stimulating the mucosal defense. Histamine H_2 receptor antagonists have become the most popular drugs for the treatment of uncomplicated duodenal ulcers, gastric ulcers, prevention of ulcer relapse and mild esophagitis. However, H_2-receptor antagonists, like other gastric antisecretory drugs, exhibit high rates of ulcer recurrence following discontinuation of therapy. These drugs therefore need to be administered continuously to patients prone to such recurrences. Omeprazole, a proton pump inhibitor, has emerged as a major drug for the treatment of severe erosive esophagitis, refractory ulcers and Zollinger Ellison syndrome. Misoprostol, a prostaglandin analog, has become one of the best drugs available for treatment and prevention of NSAID-induced ulcers. Sucralfate and organic bismuth salts exert their anti-ulcer action directly on the mucosa with little, if any, systemic absorption. Several preliminary clinical studies suggest that the co-treatment with bismuth salts and antibiotics, is associated with marked reduction of duodenal ulcer recurrences even in patients who continue their smoking habits (4). The beneficial effects of bismuth salts on ulcer recurrence is believed to be a consequence of eradication of H. pylori. The major drawbacks for bismuth salts as anti-ulcer drugs is the potential systemic toxicity (encephalopathy) and poor patient compliance because they require administration at 3 to 4 times daily and frequently with two other antibiotics in the so-called „triple" or „quadruple" therapy regimens.

We are now at a crossroad. Do we now have safe and effective medications to meet all the ideal aims of peptic ulcer therapy? Do we have good drugs to treat the complications derived from peptic ulcers or diseases caused by decreased mucosal defense? Shall we abandon the search for novel therapy of peptic ulcers? Shall we search for better antibiotics for the eradication of H. pylori? Obviously the answers to all of these questions are uncertain. Despite these facts, several major multinational pharmaceutical companies have given

up their research to discover better anti-ulcer drugs. The questions being asked now by the few active industrial and academic scientists are: what type of drugs should we now develop? Should we look for better anti-bacterial agents and/or vaccines, or should we focus on development of drugs that enhance the mucosal defense against such bacterium and other aggressive factors? We clearly do not have good drugs to treat ulcer complication such as those associated with upper gastrointestinal bleeding, drug-induced ulcer from sclerotherapy, radiation and chemotherapy. Furthermore, we do not have convenient and acceptable treatment regimens for anti-bacterial drugs needed to prevent ulcer recurrence or effective vaccines to provide a total cure should re-infection occurs.

Although the current tide in the clinical search for anti-ulcer drugs is now focused on the antibiotics approach, I believe that there are other compelling research avenues which we must simultaneously explore. Considerably interesting and exciting developments have recently surfaced regarding tissue specific growth factors such as Epidermal Growth Factor, Fibroblast Growth Factor and Platelet-derived Growth Factor (5, 6). These drugs have multiple beneficial mechanisms (cytoprotection, enhanced tissue repairs and cellular restitution) that are relevant to this disease. One of these agents had shown efficacy of healing gastric ulcers when administered only twice weekly (7).

If additional confirmatory, long-term and meaningful clinical studies establish that H. pylori eradication is the ultimate cure of peptic ulcer, then we should search for an effective, easy-to-take and safe treatment for the eradication of H. pylori. Such an approach may become the therapy of choice and might offer a cure for this perplexing disease. However, until we have the answers to these questions, we should not give up on research for uncovering better anti-ulcer drugs.

Note: The opinions expressed represent the author's own view on the subject. These are not official statements of either G. D. Searle and Co., Northwestern University, or the University of California at Los Angeles.

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