Promising new NSAID-derivative may be well-tolerated by chronic pain sufferers

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Millions of people in the U.S. use nonsteroidal anti-inflammatory drugs (NSAIDs) to treat pain and inflammation. For osteoarthritis, rheumatoid arthritis and other chronic pain conditions, NSAIDs such as naproxen (ALEVE) are often suggested as an ongoing prescription. However, stomach and intestinal problems associated with long-term use of NSAIDs limit the ability of many people to tolerate them. Previous studies have shown that circulating bile—a fluid produced in the liver to help breakdown fats in the small intestine—could contribute to NSAID-induced small intestine injury. Now, researchers have found that a new naproxen-derivative drug, ATB-346, may protect the small intestine from inflammation and ulcers by blocking harmful changes in the bile and gut bacteria that occur following NSAID use.

Long-term use of NSAIDs is associated with stomach and intestinal ulceration and bleeding. Doctors often prescribe proton pump inhibitors (PPIs) and histamine H2 receptor antagonists (H2RAs) along with long-term NSAID prescriptions to reduce the amount of harmful gastric acid secretions. While these agents can help protect the stomach and upper intestines, taking PPIs or H2RAs and NSAIDs together can actually cause even more damage to the small intestines. This leaves people with chronic symptoms who rely on NSAIDs without a pain relief option that also protects the small intestine from injury.

Hydrogen sulfide (H2S) is a naturally occurring molecule in the body that can help protect the lining of the gastrointestinal (GI) track from damaging substances—such as acid, bile and drugs—and keep levels of

gut bacteria in a healthy range. "A new class of H2S-releasing NSAID derivatives has demonstrated vastly improved GI safety, producing negligible damage in both the stomach and small intestine," wrote the multinational research team that conducted the study. "In particular, ATB-346, a H2S-releasing naproxen derivative, has demonstrated superior GI safety compared with its parent NSAID (naproxen) in circumstances in which mucosal defense is significantly impaired, even at doses many times greater than those required for anti-inflammatory effects."

The team compared the effects of naproxen and ATB-346 on the small intestine to examine how each drug affected the toxicity level of the bile, circulated in the enterohepatic (bile, liver and small intestine) circulatory system, and affected the composition of gut bacteria. The researchers gave one set of rats a commonly prescribed dosage of naproxen and another set a comparable dose of ATB-346.

Despite the dose similarity of the two drugs, the researchers found higher bile toxicity, more small intestine ulceration and inflammation and an increased presence of harmful gut bacteria (which can worsen intestinal injury and impair ulcer healing) among rats treated with naproxen. Conversely, ATB-346 did not cause intestinal damage, inflammation or an increase in the toxicity of bile, and it seemed to positively modify NSAID-related increases in harmful gut bacteria.

"When NSAIDs undergo enterohepatic recirculation, the intestinal epithelial cells are repeatedly exposed to the topical damaging effects of the NSAID and its metabolites," the researchers wrote. "Interestingly, although ATB-346 is metabolized to naproxen, the levels of naproxen in bile from ATB-346-treated rats were substantially lower than those observed in rats treated with an [equivalent] dose of naproxen, despite plasma levels of naproxen being comparable in the two groups."

Treatment with ATB-346 shows promise because it "spares the small intestine of injury … possibly because of substantially reduced biliary secretion of this drug and its metabolites, but likely also due to H2S-mediated cytoprotective and microbiota-modifying effects," they added.

More information: "Deciphering the Pathogenesis of NSAID-Enteropathy Using Proton Pump Inhibitors and a Hydrogen Sulfide-Releasing NSAID." *American Journal of Physiology - Gastrointestinal and Liver Physiology* Published 16 April 2015 Vol. no. , DOI: 10.1152/ajpgi.00066.2015

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