

Abstract Belgian Week of Gastroenterology 2018

Title: Influence of the slow-release H₂S donor GYY4137 and the H₂S-releasing naproxen derivative ATB-346 on postoperative ileus.

Introduction:

Postoperative ileus (POI), the impairment of gastrointestinal motility after abdominal surgery, is mainly due to intestinal muscular inflammation triggered by surgical handling. Hydrogen sulfide (H₂S), known as a toxic gas, has been recognized as an important mediator of many physiological processes, including inflammation and H₂S is now exploited therapeutically for its anti-inflammatory effects. The slow-release H₂S donor GYY4137 was shown to reduce gastrointestinal inflammation, but was not tested yet in POI. ATB-346 is a H₂S-releasing derivative of the non-steroidal anti-inflammatory drug (NSAID) naproxen, developed to reduce gastrointestinal injury of naproxen when applied for rheumatic conditions. NSAIDs are commonly used to treat pain and inflammation in POI, because of their opioid-sparing effects.

Aim:

The aim of this study was to investigate the effect of GYY4137, ATB-346 and naproxen on intestinal inflammation and gastrointestinal transit in POI.

Methods:

C57Bl6J mice were fasted for 7 h, anesthetized (isoflurane) and after laparotomy, POI was induced by compressing the small intestine with cotton applicators (intestinal manipulation; IM) for 5 min. GYY4137 (50 mg/kg, intraperitoneally), ATB-346 (16 mg/kg, intragastrically) or an equimolar dose of naproxen (10 mg/kg, intragastrically) were administered 1 h before IM. Gastrointestinal transit was assessed 24 h postoperatively using fluorescent imaging 90 min after fluorescein gavaging (geometric centre [GC] of gastrointestinal fluorescein progression). The small intestine was divided in 6 equal parts; mucosa-free muscularis segments were prepared and stored at -80° C for later analysis of myeloperoxidase (MPO) activity as an index of leukocyte infiltration, of the inflammatory cytokines interleukin (IL-)6, IL-1 β and monocyte chemotactic protein 1 (MCP-1), and of COX-2 and inducible NO synthase (iNOS) activity.

Results:

IM profoundly delayed transit (GC: 3.6 ± 0.5 versus 9.0 ± 0.4 in non-operated controls; mean \pm s.e.m. of $n = 8$ per group). Pre-treatment with GYY4137 (GC: 7.6 ± 0.5) and ATB-346 (GC: 8.4 ± 0.3) prevented the delayed transit seen after IM while naproxen only partially did (GC: 5.9 ± 0.5). Administration of GYY4137 and ATB-346 significantly reduced the increase in MPO activity and in IL-6, IL-1 β and MCP-1 levels in the intestinal muscularis caused by IM; the reduction by naproxen was less pronounced and only reached significance for MPO activity and IL-6 levels. All treatments significantly reduced the increase in COX-2 activity caused by IM, naproxen not being less effective than GYY4147 and ATB-346 for this parameter. Preliminary data on part of the tissues of each group suggest that GYY4137 and ATB-346 but not naproxen are able to reduce the IM-induced elevation of iNOS activity.

Conclusion:

The study shows that naproxen partially prevents POI, probably through its inhibitory effect on COX-2 activity in view of the previously established role of COX-2 in murine POI (Schwarz et al., Gastroenterology, 2001). However, both ATB-346 and GYY4137 were more effective, the result with GYY4137 showing that H₂S per se can prevent POI. The mechanism of action of the H₂S donors in POI will now be studied further.