

This Month in Gastroenterology

Jan Tack and John M. Carethers, Section Editors

A Modified and Safer NSAID for Colorectal Cancer Chemoprevention

Nonsteroidal anti-inflammatory drugs (NSAIDs) have a chemopreventive effect on the development of colorectal neoplasia, but toxicities have precluded a general recommendation for mass usage solely for this purpose. The development of safer NSAIDs that are as effective but much less toxic might allow wider utilization for the purpose of chemoprevention.

In the study by Mackenzie et al, a modification of the carboxyl moiety of the NSAID sulindac to form phospho-sulindac was done with its properties studied, including its anti-tumor effects and toxicity. Phospho-sulindac was >14.2-fold more potent than sulindac for inhibiting colon cancer cell growth

through reducing dose-dependent cell proliferation and induced concentration-dependent apoptosis, features not observed in normal colon epithelial cells. Phospho-sulindac induced oxidative stress to trigger apoptosis, and reduced the level of polyamines (particularly spermidine and spermine) by inducing SAT1 enzyme activity 4.4-fold (compared with sulindac at 2.5-fold), all of which could be blocked with *N*-acetylcysteine or siRNA to SAT1. Phospho-sulindac suppressed nuclear factor- κ B activation, but increased cyclo-oxygenase (COX) activity (and subsequent prostaglandin E₂ production) unlike sulindac that inhibits COX activity. Like the synergism between sulindac and difluoromethylornithine (DFMO) for reducing cancer growth, phospho-sulindac synergized even greater with DFMO than sulindac, reducing cell growth, inhibiting cell-cycle phase transitions, and increasing apoptosis

through more marked reduction in polyamines. Phospho-sulindac was more effective in inhibiting tumor growth in vivo over sulindac, and combining phospho-sulindac with DFMO reduced tumor burden in *Apc^{min}* mice by 90.2% over controls. Phospho-sulindac showed no genotoxicity, and showed no evidence for gastrointestinal toxicity as compared with significant toxicity and mortality with sulindac (Figure 3).

This study indicates that phospho-sulindac is more potent but safer than sulindac for colon cancer chemoprevention, and synergizes with DFMO making it more effective. Although analgesic properties were not addressed and do not have direct role for chemoprevention, modifying its carboxyl moiety and its inability to block COX suggests that any analgesia would be via a non-COX mechanism. Phospho-sulindac should be explored in humans for its chemopreventive potential.

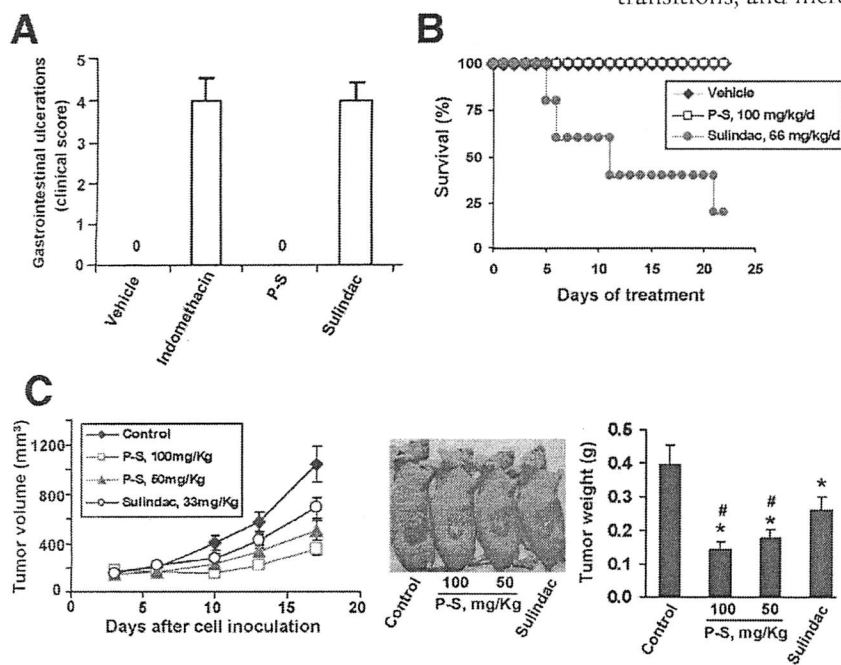


Figure 3. Phospho-sulindac (P-S) is a safe and effective antitumor agent against colon cancer in vivo. (A) Acute gastrointestinal toxicity of sulindac and P-S. Rats were treated with P-S, sulindac, indomethacin or vehicle and at day 5, the number and sizes of small intestinal ulcerations were counted and scored. (B) Survival curve for mice treated daily for 3 weeks with equimolar doses of P-S or sulindac. (C) Effect of P-S and sulindac on colon cancer xenografts in nude mice. *Left panel:* Tumor volume growth over time for each treatment. *Center panel:* Photographs of mouse xenografts. *Right panel:* Mass of dissected xenografts. All values are means + SEM. **P* < .05 versus vehicle-treated mice; #*P* < .05 versus sulindac-treated mice.