NSAID-enteropathy and intestinal microbes

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It is ironic as the financial support for research into the gastrointestinal side effects of NSAIDs has declined with a noticeable decrease in the number of original research studies being published that the pathogenesis and pathophysiological effects of NSAIDs are now increasingly understood. Independent research workers have formulated a comprehensive framework for the gastrointestinal damage, largely based on “older” studies that the more forceful “opinion leaders” at the time ignored in their persistent, single minded attempt to keep the message simple, namely the misleading message that Cox-1 and Cox-2 inhibition accounts for all the side effects and therapeutic effects of NSAIDs, respectively. This view was largely market driven, simple and easily understood which is important for the uninitiated prescribers. It is, however, an important reminder that much of what is accepted in science is still personality driven and the facts are not widely voiced until the “opinion leaders” retire from the field. Big Pharma, their servants and collaborators highlighted the gastric side effects, at the exclusion of other gastrointestinal sites, because of the potential use of their drugs that could prevent and treat the gastro-duodenal side effects alone. Nevertheless, the adverse effects of NSAIDs were much more prevalent in the small bowel than the stomach (Bjarnason et al. 1993) and the pathogenesis much more interesting (Bjarnason et al. 2018).

There is now an acknowledgement that the pathogenesis of NSAID-induced gastrointestinal damage is far more complex than simply the inhibition of COX-1 and 2. Indeed, neither mechanism plays a major part in initiating the damage. A recently proposed framework for the damage (Bjarnason

et al. 2018) can be summarised as a multi-stage pathogenic process and this involves an initial effect on mitochondria. Hence all acidic, and to a lesser extent basic COX-2 inhibitors initiate damage by a “topical” effect which involves a “detergent” action on the surface cellular phospholipids and more importantly uncoupling of mitochondrial oxidative phosphorylation following their entry into the surface cells. This, in turn, renders the intestinal cells deficient in energy sources (ATP) with predictable cellular-tissue consequences, including activation of caspases and increased mucosal permeability. At this stage, reduced levels of mucosal and circulating prostanoids, from inhibition of COX-1 and 2, plays a permissive role in modifying the cellular-tissue response to mucosal injury, and intensifies the damage, perhaps principally by preventing a compensatory increase in mucosal blood flow. The third stage then involves the tissue response which invariably includes the interaction between the luminal aggressive factors and mucosal defences. In the small bowel, where NSAIDs are mostly absorbed, the main luminal aggressive factors are bile, pancreatic secretions and, most importantly, the intestinal microbiome. Long-term effects are mostly related to immuno-pathological (T- and B-cell) responses. Although all stages of this multi-stage pathophysiological process interact with each other, each one is a potential target for development of safer anti-inflammatories as well as therapeutic intervention to minimize or reverse the damage.

A recently published review by Maseda and Ricciotti (2020), “NSAID-gut microbiota interaction” is therefore potentially of major interests because the microbiota plays such an important pathophysiological role in the small bowel damage due to these drugs. Furthermore, NSAIDs may independently alter the microbiome and collectively these changes may lead to alterations in the pharmacokinetic profiles of NSAIDs, alter their efficacy, etc.

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Maseda and Ricciotti review the ‘new’ pathogenesis of NSAID damage, but this does not add much to the original framework (Bjarnason et al. 2018).

They start off by emphasizing the importance of the symbiosis between the microbiome host interaction along traditional lines. They fall into the same trap as most in trying to justify that this interaction is mutually beneficial to the microbiome and host. It is clearly to the overwhelming benefit of the microbes that live there. We gain little benefit, if any, from their presence (the vitamins that they produce are formed in the colon where they are not absorbed, they metabolise undigested fibre, but this would be passed out in any case and the proposed importance of butyrate production as an energy supply for colonocytes grossly underestimates the adequacy of the circulation to provide nutrients, etc.). A sterile gut from birth would not then require the vast and complex immunological system that allows us to co-exist with the microbes. The bubble boy who lived in a germ-free environment and the wellbeing of germ-free animals provide further proof to the microbiome not being of much importance to the host. Lastly, the presence of the microbes plays a role in almost all colonic disease one way or the other. No bugs no disease!

Their review covers the role of the microbiome in the pathogenesis of NSAID-enteropathy and the role of activating or degrading of NSAIDs and other drugs and hence potentially affecting their efficacy and toxicity.

The former is discussed in considerable detail both in animals and man and is a good source for references for researchers or physician-scientists. The importance of the observations of the change in the microbiome following NSAIDs in animals are, however, of very doubtful importance for humans as the intestinal microbiome differ so markedly between species. Interpretation of human studies is no easier as the precise composition and alterations in the microbiome are open to so many variables that are next to impossible to control. The current techniques for assessing the microbiome are mostly done on stool and hence represent what is happening in the whole of the gastrointestinal tract and not necessarily at the site of interest.

What is not in doubt is that NSAIDs use is associated with alterations of the composition of the gut microbiome. The authors then consider whether the effect is due to a direct effect of NSAIDs on the microbes or if it is a secondary effect, namely the inevitable consequence of microbiological growth as a consequence of the cellular damage and tissue damage caused during NSAID absorption with the loss of mucosal integrity as postulated in the new pathogenic framework. One way of discriminating between the direct effect of NSAIDs on microbes (altering growth patterns and metabolic functions) and the mucosa would be to experiment on germ free animals (who do not develop macroscopic small bowel damage when administered NSAIDs), gnotobiotic animals

and even with targeted antibiotic treatment, but this has not been done to any significant extent in relation to NSAIDs (Kennedy et al. 2018). Such research will provide insights into the mechanism of damage, but again extrapolation over to humans is fraught with difficulty.

Simply focusing on the composition of the microbiome provides limited information and this can be viewed as a static morphological change (similar to histopathological changes) rather than functional one. Some illnesses may be associated with signature changes in the microbiome while the activity of a particular microbe(s) may be much more important in the pathogenesis of the NSAID damage and indeed many other intestinal disease.

Maseda and Ricciotti cover the microbiological literature comprehensively in this review. The animal studies are described and possible interpretations of the findings. However, what is needed here is an analytical review rather than a descriptive one because much of the data is contradictory and there are differences between the microbiome changes seen with different NSAIDs (Rogers and Aronoff 2016) and this has to be viewed with the knowledge that all cause similar if not identical intestinal damage. For instance, the authors cite studies that suggest that the COX-2 selective inhibitors celecoxib and rofecoxib cause small bowel damage versus no damage, respectively, in animals. Yet, COX-2 deficient animals develop consistent small bowel damage (Morham et al. 1995; Sigthorsson et al. 2002) and both drugs cause small bowel in man when taken long term (Maiden et al. 2007). Many of the cited studies include measures of downstream inflammatory cascade events which do not discriminate between the different possible actions of the NSAIDs on the mucosa and the microbiome, i.e., the difference between causative vs. correlative factor change in the damage (Kennedy et al. 2018). These authors rightly draw attention to the fact that the changes in bacterial composition of the gut with NSAIDs have been known for a long time but the precise reasons are still unknown. Current investigational lines include a possible antibacterial action of certain NSAIDs. The fear is that the subject matter will only be resolved by an integrated hypothesis-driven research involving germ free-gnotobiotic and antibiotic treated animal models. This is an expensive journey and the findings may not be applicable to humans.

The human studies are again well described with up to date citations of studies that examine the gut microbiome and NSAID use. The shortcomings of these studies are highlighted and this section provides a good basis for those who contemplate such research. Again, a word of warning from past experiences. Every new revolutionary methodology in the past, such as the idea that sequencing proteins, characterising the immunology or genetic pattern of disease, mapping the human genome, etc., have promised spectacular therapeutic interventions if not a cure for disease. Yet very few

have materialized and the promises of the use of new technology of mapping the human microbiome is no different. When substantial shifts and alterations of the human microbiome is evident in certain disease there is unfortunately no available methodology to specifically reverse the changes. If NSAID alter the intestinal microbiome as a consequence of the cellular damage and increased exposure of luminal bacteria to the mucosa (hence potentiating the damage) it is not likely that antibiotics will have a role in preventing the damage because each dose of NSAID will continue to cause damage and long-term antibiotics are fraught with difficulties. Although we cannot 'normalise' the intestinal microbiome in NSAID-enteropathy there is no reason why certain probiotics might not have a potential benefit, by shifting the microbiome from an aggressive to a less aggressive one. Although certain probiotics, such as Symprove[®], appear to have certain beneficial characteristics over other commonly available ones for stability, resistance to acid digestion and ability to colonise the intestine (Fredua-Agyeman and Gaisford 2015) the choice of probiotic for the prevention and treatment of NSAID enteropathy cannot be predicted and will depend on the results of adequately designed studies. There are very few such studies and most are limited to low dose aspirin ingestion. Accordingly, a Bifidobacterium preparation protected against aspirin-induced enteropathy (Mortensen et al. 2019), as did *Lactobacillus gasseri* (Suzuki et al. 2017) while another *Lactobacilli* preparations had no significant effect on mucosal integrity (Mujagic et al. 2017). VSL-3 had a modest effect in the short term (Montalto et al. 2010). The acceptance of a particular probiotic for the prevention and treatment of NSAID-enteropathy will only come from randomised clinical trials in patients and the extrapolation of efficacy of one probiotic to another should not be accepted.

The idea that individual NSAIDs may have a preferential effect on intestinal bacteria, e.g., that the bacteria may metabolise the NSAID to alter their efficacy and toxicity is an important issue which is in need of further studies. However, all conventional NSAIDs seem to be associated with a similar prevalence and severity of small bowel damage in man when taken long term and tolerance to their therapeutic effect is certainly not a commonly encountered problem in routine practice. Additionally, application of in vivo ³¹P NMR and related high-resolution spectroscopic procedures may be useful for tracing or tracking intermediary metabolites and enable effects of the NSAIDs on metabolism in mucosal cells and components of the microbiome to be discriminated.

It is difficult to predict how the issue of NSAID-induced gastrointestinal toxicity and the microbiome is going to develop. The new technology of characterising the microbiome in man will undoubtedly yield a lot of data, but the interpretation of any changes are difficult to assess as

this research is essentially a fishing expedition rather than hypothesis driven.

The prevention and treatment of NSAID enteropathy is a difficult issue. There are no measures as yet to prevent the initiation of the damage due to uncoupling of mitochondrial oxidative phosphorylation, so intervention needs to focus on the downstream inflammatory processes. Treatment with certain antibiotics has some effect, but only whilst co-administered with the NSAIDs (Scarpignato et al. 2016). The role of probiotics, that can be taken long term without apparent adverse effects is a real possibility. However, their development is somewhat hampered by "armchair speculants" within the regulatory authorities.

Hence, health claims that imply a cause-effect relationship between a food/ingredient and health are regulated by the European Food Safety Authority (EFSA) (EFSA health claims 2016). The definition of what constitutes a health relationship is challenging, and in the case of probiotics, the health claim is considered to be incorporated into its definition 'live microorganisms which when administered in adequate amounts confer a health benefit on the host' (FAO/WHO) (FAO/WHO 2001). Additionally, the scope of health claims focuses on healthy populations, despite the fact the majority of probiotic research focuses on disease.

EFSA has not approved any probiotics for prevention or treatment of disease despite positive results from a number of rigorously controlled randomized clinical trials. Indeed, this has led to the term 'probiotic' being banned from use for marketing purposes, resulting in confusion and mistrust amongst the general public.

In the UK, probiotics are not classified as a food or a medicine but as a food supplement. Hence the probiotics do not fall within the scope of the Medicines and Healthcare products Regulatory Agency (MHRA). Instead, The Advisory Committee on Borderline Substances (ACBS) is responsible for assessing and recommending products (including probiotics) for prescription within the NHS (Part XV of the Drug Tariff). However, The MHRA and ACBS position is that the use of 'probiotics' to prevent or treat a clinical condition would likely be considered a specific medicinal claim under the MHRA. Given this NICE approval would not be forthcoming and has not been so even for conditions such as for the Irritable Bowel Syndrome where there is substantial amount of data to show efficacy. General physicians who are faced with underfunded drug budgets for prescription drugs are able to prescribe some probiotics, but the reality is that very few do so because of the extra cost which their funding bodies will not take into account when determining their budgets. It is therefore probable that even if probiotics were demonstrated to reverse the small bowel damage due to NSAIDs and hence prevent the complications and mortality of NSAID-enteropathy that the enormous cost of conducting randomized clinical trials may not be easily recovered

and this will detract even the most enthusiastic probiotic providers.

References

- Bjarnason I, Hayllar J, Macpherson AJ, Russell AS (1993) Side effects of nonsteroidal anti-inflammatory drugs on the small and large intestine. *Gastroenterology* 104:1832–1847
- Bjarnason I, Scarpignato C, Holmgren E, Olszewski M, Rainsford KD, Lanås A (2018) Mechanisms of damage to the gastrointestinal tract from nonsteroidal anti-inflammatory drugs. *Gastroenterology* 154:500–514
- EFSA Health Claims (2016) EU register of nutrition and health claims made on food. https://ec.europa.eu/food/safety/labelling_nutrition/claims/register/public/?event=register.home
- FAO/WHO (2001) <https://www.fao.org/3/a-a0512e.pdf>
- Fredua-Agyeman M, Gaisford S (2015) Comparative survival of commercial probiotic formulations: tests in biorelevant gastric fluids and real-time measurements using microcalorimetry. *Benef Microbes* 6:141–151
- Kennedy EA, King KY, Baldridge MT (2018) Mouse microbiota models: comparing germ-free mice and antibiotics treatment as tools for modifying gut bacteria. *Front Physiol*. <https://doi.org/10.3389/fphys.2018.01534>
- Maiden L, Thjodleifsson B, Seigal A, Bjarnason II, Scott D, Birgisson S, Bjarnason I (2007) Long-term effects of nonsteroidal anti-inflammatory drugs and cyclooxygenase-2 selective agents on the small bowel: a cross-sectional capsule enteroscopy study. *Clin Gastroenterol Hepatol* 5:1040–1045
- Maseda D, Ricciotti E (2020) NSAID-gut microbiota interactions. *Front Pharmacol* 11:1153. <https://doi.org/10.3389/fphar.2020.01153>
- Montalto M, Gallo A, Curigliano V, D'Onofrio F, Santoro L, Covino M, Dalvai S, Gasbarrini A, Gasbarrini G (2010) Clinical trial: the effects of a probiotic mixture on non-steroidal anti-inflammatory drug enteropathy - a randomized, double-blind, cross-over, placebo-controlled study. *Aliment Pharmacol Ther* 32:209–214
- Morham SG, Langenbach R, Loftin CD, Tiano HF, Vouloumanos N, Jennette JC, Mahler JF, Kluckman KD, Ledford A, Lee CA, Smithies O (1995) Prostaglandin synthase 2 gene disruption causes severe renal pathology in the mouse. *Cell* 83:473–482
- Mortensen B, Murphy C, O'Grady J, Lucey M, Elsaft G, Barry L et al (2019) *Bifidobacterium breve* Bif195 protects against small-intestinal damage caused by acetylsalicylic acid in healthy volunteers. *Gastroenterology* 157:637–646
- Mujagic Z, De Vos P, Boekschoten MV, Govers C, Pieters HJ, De Wit NJ et al (2017) The effects of *Lactobacillus plantarum* on small intestinal barrier function and mucosal gene transcription: a randomized double-blind placebo controlled trial. *Sci Rep* 7:40128. <https://doi.org/10.1038/srep40128>
- Rogers MAM, Aronoff DM (2016) The influence of non-steroidal anti-inflammatory drugs on the gut microbiome. *Clin Microbiol Infect* 22(2):178.e1–178.e9. <https://doi.org/10.1016/j.cmi.2015.10.003>
- Scarpignato C, Dolak W, Lanås A, Matzner P, Renzulli C, Grimaldi M, Zeitlinger M, Bjarnason I (2016) Rifaximin reduces number and severity of intestinal lesions associated with use of non-steroidal anti-inflammatory drugs in humans. *Gastroenterology* 152:980–982.e3. <https://doi.org/10.1053/j.gastro.2016.12.007> (Epub 2016 Dec 19)
- Sigthorsson G, Simpson RJ, Walley M, Anthony A, Foster R, Hotz-Behoftsitz C, Palizban A, Pombo J, Watts J, Morham SG, Bjarnason I (2002) COX-1 and 2, intestinal integrity, and pathogenesis of nonsteroidal anti-inflammatory drug enteropathy in mice. *Gastroenterology* 122:1913–1923
- Suzuki T, Masui A, Nakamura J, Shiozawa H, Aoki J, Nakae H et al (2017) Yogurt containing *Lactobacillus gasseri* mitigates aspirin-induced small bowel injuries: a prospective, randomized, double-blind, placebo-controlled trial. *Digestion* 95:49–54

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