



Original Research Article

NO CHANCE TO FACE NSAIDs THREATENING?

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Non Steroidal Anti-Inflammatory Drugs (NSAIDs), are widely used as first line of defense against most of acute and chronic inflammatory diseases. However, in spite of their apparent safer profile, as compared to steroids, they can also drive into moderate and severe reactions. Since the very beginning foremost concerns have been focused on the Gastric Damage coming from the inhibition of COX-1 derived prostaglandins, which were found to play a fundamental protective action on the overall stomach homeostasis [1]. Thereafter indeed, most efforts to improve NSAIDs therapeutic proficiency were aimed at counteracting upper Gastrointestinal (GI) adverse reactions.

In this regard, the concomitant administration of Proton Pump Inhibitors (PPI) in a way of reducing hyperacidity and consequently counterbalancing the associated incidence of heartburn, ulcers and bleeding, was one of the first and till nowadays most used approaches. Nonetheless, in spite of the actual clinical benefit in terms of gastric disturbances, on the other hand it has been noticed that long term treatment with PPI might lead to an impairment on minerals and vitamins absorption [2] as well as on enteric microbiota equilibrium [3], driving therefore into many other systemic disturbances.

In order to bypass such adverse events, a parallel approach, triggering alternative compensatory mechanisms while avoiding to negatively impact on Calcium and microbiota homeostasis, was pursued by developing novel NSAID molecules harboring a Nitric Oxide (NO) releasing moiety. Upon endogenous enzymatic cleavage, the NO releasing moiety would provide a series of favorable compensatory actions to preserve gastric safety [4]. These dual action hybrid molecules, belonging to a new class of drugs called CINODs (COX Inhibitors Nitric Oxide Donors), were encouraging in fact large expectations.

However, a third approach in parallel faced the problem from a different and apparently much clever and radical point of view. Rather than triggering compensatory mechanisms to counteract NSAIDs derived Gastric Damage the novel strategy developed a new class of NSAIDs with a very specific Cyclooxygenase inhibitory activity: active on COX2 but not on COX1. In such a way the novel chemical entities would retain anti-inflammatory actions by inhibiting COX2 while on the other side they would be deprived of GI concerns as unable to inhibit the beneficial COX1 derived Prostaglandins in the stomach. As a matter of fact, given the early successful results from this third approach, at that time CINODs became much less attractive and their development was almost discontinued.

Unexpectedly however, short after that it was noticed that following chronic treatment with COXIBs it was registered a relevant increase on severe and fatal cardiovascular events. Indeed, as later emerged from several studies it was realized that whereas COX2 specific inhibitors might indeed provide a better upper GI safety profile, on the other hand, within the vascular environment it might be deleterious mainly in patients suffering from endothelial dysfunction [5].

At this point, reconsidering the ubiquitous regulatory potential of NO, it resulted opportune to “rescue” CINODs. Actually favorable NO compensatory mechanisms are not limited to the upper GI Tract but also on the Vascular Bed. A balanced COX inhibition while providing exogenous NO donation may grant a much safer Cardio-Vascular profile [6]. Moreover an adequate NO releasing pattern could provide an extra benefit by synergizing with the anti-inflammatory actions from the NSAID parent drug [7,8]. Unfortunately however, spitefully of the very strong rational and the large and robust preclinical evidence, the favorable results obtained on the main clinical trial carried out by a relative small biotech (NicOx Spa) [9] were not convincing enough to the FDA and were soliciting for further

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investment. An adequately extended population size, a more appropriate identification of patients subpopulation target as well as much more accurate definition of clinical end points and biomarkers, would be strongly recommended in order to unequivocally convince regulatory authorities. Moreover, last but not least, further attention should be also invested on the incidence and relevance of NSAIDs adverse effect on the Lower Intestinal Tract. Contrary to PPI co-administration and COXIBs approaches, CINODs might exhibit a much safer profile in terms of NSAIDs derived Lower Intestinal Damage [10], avoiding therefore many other associated systemic disturbances.

It is obvious that facing such kind of extended and complex clinical trials is an endeavor that might require great investments, but on the other side continuing to face huge NSAIDs adverse effects is certainly much more expensive in all sense to the whole society.

Therefore, considering altogether the strong scientific rational, the robust preclinical data and the favorable clinical results so far collected, it might worth wondering whether to further pursue the NO approach in order to globally face the insidious and large spectrum of NSAIDs threatening.

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