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Non-steroidal Anti-inflammatory Drugs (NSAIDS): Chemistry, Mechanism and their Adverse events.

Rajiv Tonk [1], Sumit Tewatia[2], Shafqat Majeed [2], Manish Dagar [2]
1. Deptt. of Pharm. Chemistry, SPS Delhi Pharmaceutical Sciences & Research University, Saket, New Delhi 110017
2. SPS Delhi Pharmaceutical Sciences & Research University, Saket, New Delhi 110017

ABSTRACT

More than 15 different non-steroidal anti-inflammatory drugs (NSAIDs) are available commercially, and these agents are used worldwide for their analgesic antipyretic and anti-inflammatory effects in patients with multiple medical conditions. NSAIDs, including aspirin, do not generally change the course of the disease process in those conditions, where they are used for symptomatic relief. The main mechanism of action of NSAIDs is the inhibition of the enzyme cyclooxygenase (COX). Cyclooxygenase is required to convert arachidonic acid into thromboxane's, prostaglandins, and prostacyclin's. Assessment of toxicity and therapeutic response to a given NSAID must take into account the time needed to reach the steady state plasma concentration (roughly equal to three to five half-lives of the drug). NSAIDs have well-known adverse effects affecting the gastric mucosa, renal system, cardiovascular system, hepatic system, and hematologic system.

Keywords: Cyclooxygenase, NSAIDS, adverse effects.

*Corresponding Author Email: tewatiasumit000777@gmail.com
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INTRODUCTION

Traditional NSAIDs are currently used for the treatment of inflammatory disorders. However, these drugs generate serious adverse effects limiting their therapeutically benefits in the gastrointestinal tract[1]. NO-NSAIDs are the last development in the list of advances including enteric-coated tablets, prodrugs and selective COX-2 inhibitors which are created to prevent the gastric side effects of NSAIDs. The property of NO-NSAIDs is to reduce the gastrointestinal toxicity of NSAIDs by releasing NO. Various mechanisms highlight the gastric protective effect of NO including vasodilatation of local mucosal blood vessels[2]. A number of new NO secreting molecules attached to the core molecule without any pharmacological and chemical relations with NSAIDs have been recently synthesized. The objective is to define a new molecule with an improved pharmacological profile, stronger therapeutically effect and less toxic effect. Within this context, experimental trials using animal models were executed for both acute and chronic pain treatment. Various new strategies were developed for the production of LOX/COX inhibitors with this dual effect such as selective or non-selective COX inhibitors and hybrid molecules releasing nitric oxide to decrease the side effects of NSAIDs[3]. Recent data indicate serious cardiovascular side effects of selective COX-2 inhibitors and in addition, these drugs have no impact on established gastric ulcer though preventing the occurrence of new ones. In these trials, formation of hybrid molecules with nonselective COX inhibitors and the NO donor is one of the most promising strategies, because nitric oxide supports the endogenous GIT defense mechanism via its protective effects such as increasing mucus, secreting bicarbonate, increasing mucosal blood flow and decreasing proinflammatory cellular activation. In addition, NO provides a protection against the adverse effects of COX-2 via its cardiovascular activity[4]. Among NO-NSAIDs thus formed, nitro Diclofenac, nitro aspirin, nitro flurbiprofen and nitro ketoprofen were tested in clinical trials (Figure (1)). Furoxan, oxime, hydrazide and organic nitrates are nitric oxide donors used in the validation of this concept. However, long-term safety profile of these components is currently investigated. Based on these data, hybrids and prodrugs releasing nitric oxide with anti-inflammatory, analgesic and ulcerogenic properties are combined with nitric oxide donors as organic nitrates and oximes to gain new molecules. Six derivatives with the general formula of 2/4-(7-trifluoromethylquinolin-4-ylamino) benzoic acid N-(nitrooxyacetyl/propionyl) hydrazide and oxime derivatives with the formula of 1-[4-(7-trifluoromethylquinolin-4-yl-amino) phenyl) ethanol (Figure. (2)) and tested their capacity of nitric oxide release in vivo and anti-inflammatory, analgesic and ulcerogenic properties. 2-(7-

Trifluoromethylquinolin-4-yl-amino) benzoic acid-N-(2-nitrooxypropionyl) hydrazide was more potent than indomethacin which is used as standard anti-inflammatory drug. Some compounds were reported devoid of gastric ulcer tendency[5]. In addition, nitric oxide contributed to the excellent safety profiles of these compounds.

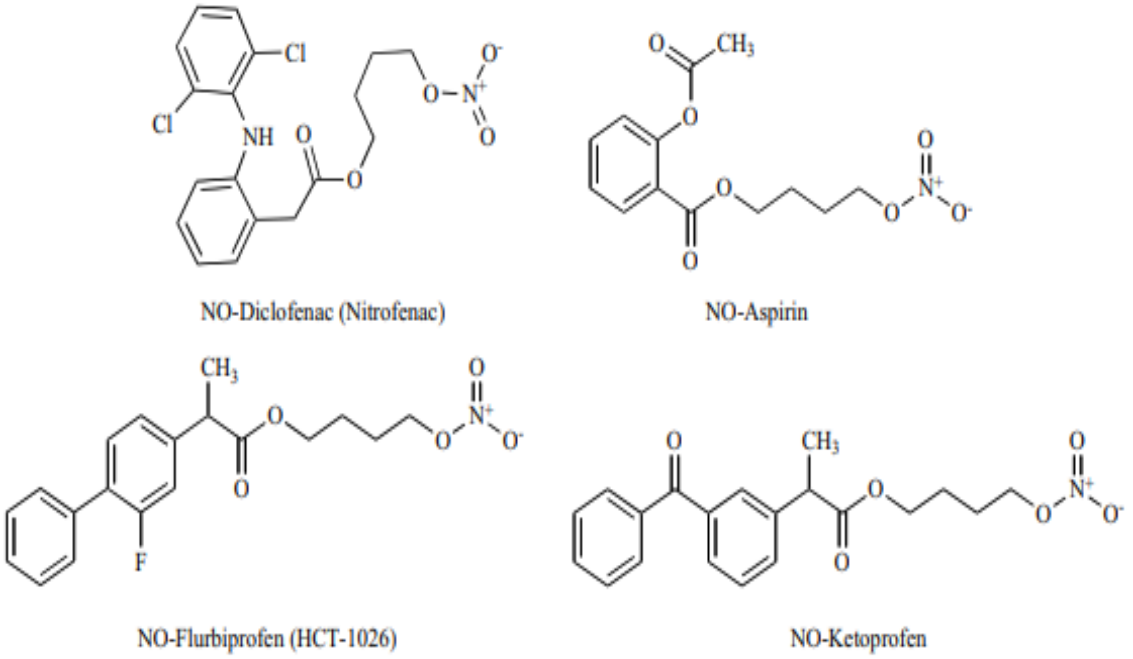

Figure 1: Conservative NSAIDs examples combined with NO.

naphthyl)} propanoate was chosen to show that glycosamide nitrate could be bioactivated to release NO. Based on these data, naproxen glycosamide nitrate prodrugs appear to be the safest alternative to naproxen sodium in the treatment of inflammatory diseases and pain. Gastrointestinal safety of naproxen and [4-(Nitrox] butyl-(2S)-2-(6-metoxy-2-naphthyl) propanoate] (AZD3582) were conducted[6]. These studies are currently at the terminal period of phase II and global marketing activities have already started. Also, developed by French Pharmaceutical company NicOx SA, Naproxcinod (HCT 3012) [(S)-6-methoxy--methyl-2-naphthaleneacetic acid 4- (nitrooxy) butyl ester is currently at the investigation stage[7]. This compound is the company's lead product and in phase III synthesized the nitric oxide derivatives of tolphenamic acid (TA)[8]. In this trial, several TA derivatives esterified with nitro oxyalcohol were synthesized and their anti-inflammatory activities, NO releasing property and anti-oxidant effects were evaluated and finally their gastrointestinal toxicities were compared[9].

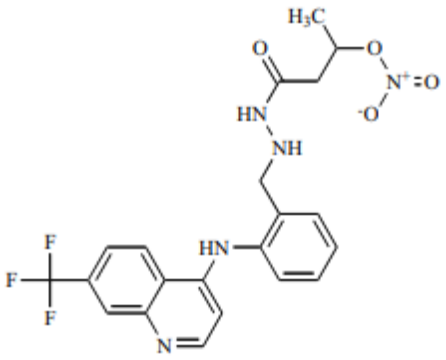

Figure 2: 2-(7-Trifluoromethylquinolin-4-yl-amino) benzoic acid-N- (2-nitrooxypropionyl) hydrazide.

DISCUSSION

Differences in anti-inflammatory activity between NSAIDs are small, but there is considerable variation in individual response and tolerance to these drugs. About 60% of patients will respond to any NSAID; of the others, those who do not respond to one may well respond to another[10, 11]. Pain relief starts soon after taking the first dose and a full analgesic effect should normally be obtained within a week, whereas an anti-inflammatory effect may not be achieved (or may not be clinically assessable) for up to 3 weeks.[12] If appropriate responses are not obtained within these times, another NSAID should be tried. The widespread use of NSAIDs has meant that the adverse effects of these drugs have become increasingly common. Use of NSAIDs increases risk of a range of gastrointestinal (GI) problems, kidney disease and adverse cardiovascular events. As commonly used for post-operative pain, there is evidence of increased risk of kidney complications[13]. Their use following gastrointestinal surgery remains controversial, given mixed evidence of increased risk of leakage from any bowel anastomosis created. An estimated 10–20% of NSAID patients experience indigestion[14]. In the 1990s high doses of prescription NSAIDs were associated with serious upper gastrointestinal adverse events, including bleeding. Over the past decade, deaths associated with gastric bleeding have declined. NSAIDs, like all medications, may interact with other medications. For example, concurrent use of NSAIDs and quinolones may increase the risk of quinolones' adverse central nervous system effects, including seizure. There is an argument over the benefits and risks of NSAIDs for treating chronic musculoskeletal pain. Each drug has a benefit-risk profile and balancing the risk of no treatment with the competing potential risks of various therapies is the clinician's responsibility.

If a COX-2 inhibitor is taken, a traditional NSAID (prescription or over-the-counter) should not be taken at the same time[15]. In addition, people on daily aspirin therapy (e.g., for reducing

cardiovascular risk) must be careful if they also use other NSAIDs, as these may inhibit the cardio protective effects of aspirin[16, 17]. Rofecoxib (Vioxx) was shown to produce significantly fewer gastrointestinal adverse drug reactions (ADRs) compared with naproxen[18]. The study, the VIGOR trial, raised the issue of the cardiovascular safety of the coxibs. A statistically significant increase in the incidence of myocardial infarctions was observed in patients on Rofecoxib[19]. Further data, from the approve trial, showed a statistically significant relative risk of cardiovascular events of 1.97 versus placebo-which caused a worldwide withdrawal of Rofecoxib in October 2004[20]. Use of methotrexate together with NSAIDS in rheumatoid arthritis is safe, if adequate monitoring is done.

CONCLUSION

Because conservative NSAIDs generate serious adverse effects limiting their therapeutically benefits in the gastrointestinal region, new trials are being done to find out a new molecule with an improved pharmacological profile, a stronger therapeutically effect or a less toxic effect. The trials collected in this paper prove that NO releasing NSAIDs demonstrate these features because of NO molecule's extraordinary structure

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