Review

Pharmacological basis for the therapy of pain and inflammation with nonsteroidal anti-inflammatory drugs

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Abstract

Nonsteroidal anti-inflammatory drugs (NSAIDs) belong to the most frequently used drugs. The discovery of an inducible isoform of cyclo-oxygenase (COX-2) has led to an intensive worldwide search and the introduction of selective COX-2 inhibitors. In this review, recent advances in understanding the mechanism of action of NSAIDs and, in this context, clinical findings on NSAID-induced gastrointestinal side effects are summarized. This knowledge is important for the effective treatment of pain and inflammation, as well as for preventing serious and sometimes lethal gastrointestinal side effects.

Keywords: COX-2 selective inhibitors, cyclo-oxygenase, gastrointestinal side effects, nonsteroidal anti-inflammatory drugs

Introduction

With a total of 97 million prescriptions per year in Germany alone, analgesic and anti-rheumatic drugs are the foremost medication in terms of frequency of use. Every day they are taken by more than 30 million people worldwide; of these, 40% of consumers are older than 60. Only 4.5% of the prescriptions are for so-called centrally acting analgesics, namely the opioids. Population studies have shown that 10–20% of all people who are 65 years or older either are currently receiving or have recently received a prescription for nonsteroidal antirheumatic drugs. During the next 20 years the number of people over 65 is expected to increase from 380 million to 600 million. The very frequent use of NSAIDs is based on the fact that these agents have many indications for which a large number of patients exist. These indications include chronic polyarthritis, psoriatic arthritis, ankylosing spondylitis, osteoarthritis, gout, inflammatory soft tissue rheumatism, low back pain, postoperative and post-traumatic inflammation, thrombophlebitis and vasculitis.

The history of analgesic and anti-inflammatory substances started with the use of decocted salicylate-containing plants by ancient Greek and Roman physicians. Willow bark was already mentioned in the Corpus Hippocraticum (a collection of medical scripts compiled by Alexandrian scholars in approximately 300 BC) as a substance for treating fever and pain conditions. Over the past 140 years other substances have been introduced for therapy, collectively termed nonsteroidal anti-inflammatory drugs (NSAIDs), after PS Hench discovered the anti-inflammatory properties of glucocorticoids in 1949. NSAIDs, which possess

COX = cyclo-oxygenase; GI = gastrointestinal; NSAID = nonsteroidal anti-inflammatory drug; PGE_2 = prostaglandin E_2; PGG = prostaglandin G; PGH = prostaglandin H..

analgesic, anti-inflammatory and antipyretic properties, are a heterogeneous group of substances without any uniform chemical properties (although most are organic acids), but nevertheless share the same therapeutic and side effects. In the past few years there have been significant advances in explaining the mechanism of action of NSAIDs.

Mechanism of action of NSAIDs

In the 1930s, Goldblatt and von Euler showed that human seminal fluid contained a component that reduced blood pressure, the effects of which could not be classified among the tissue hormones known at the time. Von Euler termed these new, unknown substances 'prostaglandins' because he presumed that these mediators were produced in the prostate [1,2]. After Bergström and Sjövall achieved the first chemical identification of a prostaglandin at the beginning of the 1960s, the era of prostaglandin research began [3]. It turned out that these hormones could be synthesized by many mammalian cells and that they participate in the regulation of numerous physiological functions.

Another milestone was the discovery by Vane and coworkers that the analgesic, antipyretic and anti-inflammatory properties of acetylsalicylate were based on the inhibition of prostaglandin synthesis [4]. Vane showed that the acidic anti-inflammatory analgesics decreased proinflammatory prostaglandin concentrations by inhibiting cyclo-oxygenase. This finding made sense because the prostaglandins characterized in the 1960s were found to be substantially involved in bringing about and maintaining inflammatory processes by increasing vascular permeability and amplifying the effects of other inflammatory mediators such as kinins, serotonin and histamine. Prostaglandin E_2 (PGE_2) is also involved in the induction of fever. As we now know, prostaglandins are not themselves significant mediators of pain; instead, they increase the sensitivity of nociceptors to other stimuli in traumatized tissue. They switch normally non-excitable polymodal receptors ('silent nociceptors') into a state in which they are easily excitable.

The biosynthesis of prostaglandins

Cyclo-oxygenase, also known as prostaglandin H synthase (PGH synthase), catalyzes the conversion of arachidonic acid (hydrolytically liberated from membrane phospholipids) to the prostaglandin endoperoxides PGG_2 and PGH_2, with the addition of two oxygen molecules. In this pathway two reaction steps can be differentiated, catalyzed by different domains of the cyclo-oxygenase protein. The first is the cyclo-oxygenase reaction (in which the formation of a C_5 ring system occurs, leading to the formation of PGG_2), and the second is the peroxidase reaction (in which the peroxide group at C-15 is reduced to an alcohol with the formation of PGH_2). PGH_2 is the precursor for the biologically active prostaglandins and thromboxanes. NSAIDs inhibit only the cyclo-oxygenase reaction of the PGH synthase.

Physiology and pathophysiology of prostaglandins

Prostaglandins are formed in numerous types of cell within an organism. Their effects are complex and depend on the type of target cells, among other factors. For this reason it is difficult to generalize the physiological roles of individual prostaglandins, because the same compound can sometimes exert even opposite effects on different types of target cell. Prostaglandins are important in the regulation of thrombocyte aggregation, inflammatory processes, pain and fever induction, the regulation of vessel perfusion, and many other processes. From these properties one can deduce the spectrum of activity of prostaglandin biosynthesis inhibitors such as indomethacin, ibuprofen and acetyl salicylic acid: NSAIDs function as anti-inflammatory, antipyretic and analgesic substances. According to the mechanism of action put forward by Vane, the unwanted side effects of NSAIDs can also be explained [eg erosion and bleeding in the gastrointestinal (GI) tract, kidney function disorders, disturbance of blood coagulation], which arise from a blockade of the physiological effects of prostacyclin, PGE_2 and thromboxane A_2 (Fig. 1). In this way, the ulcerogenic activity of NSAIDs can be derived from the physiological functions of PGE_2 and prostacyclin. Both tissue hormones are cytoprotective towards the stomach: they stimulate the production of mucus and inhibit acid secretion. NSAIDs inhibit endogenous prostaglandin synthesis and in this way remove this cytoprotective effect; thus, the induction of ulcers is promoted.

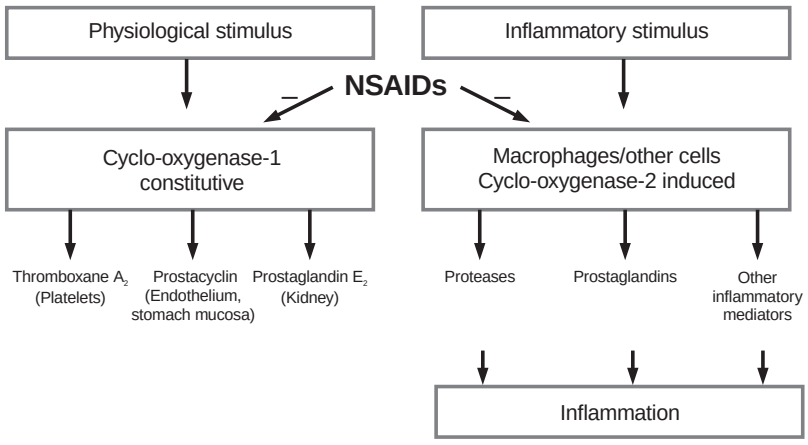
Pharmacokinetic effects on the mechanism of action

Accumulation of the acid nonsteroidal anti-inflammatory/analgesic compounds occurs particularly in inflamed tissue, in the GI mucosa, in the renal cortex, in the blood and in bone marrow owing to their acidic nature (pK_a 3–5.5) and their high capacity for binding proteins (more than 90%) [5–7]. This property is considered to be a decisive factor not just for their anti-inflammatory properties but also for the previously mentioned unwanted effects of these substances. In chronically inflamed pulmonary tissue, NSAIDs lead to an increased production of leukotrienes and in this way to asthma-like reactions due to the inhibition of prostaglandin synthesis [8]. With non-acid, neutral (paracetamol) or weakly basic (phenazone and derivatives) analgesics that do not accumulate in damaged tissue [9] but reach relatively high concentrations in the central nervous system, such side effects are either not noticed or are only marginally so. Consistent with these findings are observations that paracetamol and phenazone are only weak inhibitors of prostaglandin synthesis in the periphery [4,10], whereas paracetamol interferes with prostaglandin synthesis in the central nervous system [11].

NSAIDs as inhibitors of cyclo-oxygenase-1 and cyclo-oxygenase-2

In 1990, the first evidence for the existence of an inducible isoform of cyclo-oxygenase (COX) was published by the

Figure 1

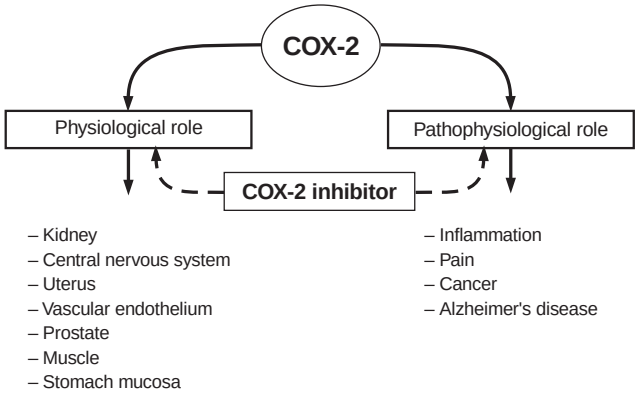


Regulation of prostaglandin biosynthesis by cyclo-oxygenase-1 and cyclo-oxygenase-2 [16].

group of P Needleman [12,13]. Structural analysis showed that the isoenzymes COX-1 and COX-2 had an amino acid sequence homology of approximately 60%. However, the isoforms encoded by different genes differ in their tissue distributions and regulation of expression. COX-1 is expressed constitutively in almost all cell types, including thrombocytes and those present in kidney, stomach and vascular endothelium, and is synthesized and regulated as a so-called 'housekeeping enzyme' involved in physiological adaptation (Fig. 1). COX-2 in contrast is inducible; induction can occur during tissue damage or inflammation in response to cytokines (tumour necrosis factor-α, interleukin-1), mitogens and growth factors. The induction of COX-2 has been observed in macrophages and monocytes, endothelial cells, chondrocytes and osteoblasts. An increased COX-2 level has also been registered in the synovial tissue of patients with rheumatoid arthritis and osteoarthritis [14]. These first findings led to the hypothesis (Fig. 2) that a selective blockade of the COX-2 isoform should lead to the inhibition of inflammation and pain without impeding the COX-1-dependent effects in the GI tissue and kidney, and in blood coagulation [16]. This hypothesis led to an intensive worldwide search for selective COX-2 inhibitors; since 1999 rofecoxib (Vioxx®) and celecoxib (Celebrex®) have been available on the markets.

In the quest for selective COX-2 inhibitors, a number of established NSAIDs (etodolac, meloxicam, nabumetone) rather surprisingly showed a seemingly selective inhibition of COX-2 [17–19]. However, further studies revealed that the COX-1–COX-2 selectivity of a test substance varied significantly depending on the test system (isolated enzymes, cell homogenates, cell lines or isolated cells) and the experimental conditions (incubation time or stimulus used). The full blood assay described by Patrono and coworkers [20] has proved to be a valuable method for determining the COX-1–COX-2 selectivity of a compound in clinically relevant human blood cells (thrombocytes and monocytes). Studies with this new assay have finally shown that none of the NSAIDs used previously selectively inhibited COX-2, in other words under therapeutic conditions it allowed thrombocyte aggregation and thromboxane synthase to be kept intact while the formation of PGE_2 after an inflammatory stimulus was suppressed. Some substances (diclofenac-Na, meloxicam and nimesulide) can at best be described as 'preferential' inhibitors of COX-2. Because the COX inhibitor concentrations were determined in the 1970s and 1980s primarily on preparations containing COX-1 (eg sheep seminal vesicle microsomes), we now have a rather late explanation of why the NSAID plasma level required to achieve an anti-inflammatory effect is far greater than that required to inhibit COX *in vitro*.

Figure 2



Physiological and pathophysiological functions of cyclo-oxygenase-2. Modified according to [15].

Recent findings on the physiological and pathophysiological role of COX-2

According to recent studies, the simple concept that COX-2 is exclusively a pro-inflammatory enzyme can no longer be considered valid [21,22]. Such studies have shown that COX-2 is constitutively expressed in brain and spinal cord, for example (Fig. 2). COX-2 is also expressed at different time points during early pregnancy within the mouse uterine epithelium: the enzyme has a role both in angiogenesis (required to build up the placenta) and nidation (of the fertilized eggs) [23]; the use of COX-2 inhibitors is contraindicated in pregnancy. COX-2 is also expressed during wound healing and has been found at the base of ulcer wounds. In this way, COX-2 inhibitors can delay the healing of ulcers and might therefore be unsuitable for patients with pre-existing ulcers [24]. Experiments on animals have shown a delay in wound healing, possibly due to an inhibition of angiogenesis associated with COX-2-induced effects on growth factors [25]. A potential clinical relevance here might be the use of selective COX-2 inhibitors for treating postoperative pain.

Numerous recent findings suggest that selective COX-2 inhibitors might open up a wide spectrum of new indications for NSAIDs. The degeneration of large areas of the brain in Alzheimer's disease is supposed to occur with the involvement of COX-2 [26]. Selective COX-2 inhibitors might also be directed towards the therapy of colorectal carcinomas [27], whereas other results show that gastric and breast carcinomas also show increased expression rates of COX-2 [28,29], so that selective COX-2 inhibitors might also be therapeutically useful for treating those tumours [30]. Recently the US FDA approved celecoxib for the treatment of the potentially life-threatening and rare genetic disorder called familial adenomatous polyposis. Animal experiments have shown that COX-2 inhibitors decelerate angiogenesis and tumour growth in a dose dependent manner [31]. Here, COX-2 seems to be expressed primarily in the newly created blood vessels (especially in the endothelial cells) needed for tumour growth.

GI side effects of NSAIDs

COX-2-selective NSAIDs were developed with the intention of reducing the unwanted side effects of NSAIDs, particularly those relating to the GI system. NSAIDs that are not COX-2 selective produce GI side effects in between 20% and 40% of all individuals who take them. The extent of this disease, known as NSAID-gastropathy, varies considerably from asymptomatic mucosal damage that is detectable only with an endoscope, through gastric pain, heartburn and dyspepsia, to life-threatening, bleeding, gastric or duodenal ulcers. Older women are more predisposed than older men towards developing an NSAID-induced ulcer, in which the stomach is more often involved than the duodenum. Here it must be emphasized that anamnestic, symptomatic and endoscopic findings are only moderately correlated [32]. In more than 10–20% of patients, the first manifestation of an NSAID gastropathy can be a severe GI complication [33].

Short-term studies (several weeks) have demonstrated that asymptomatic mucosal damage is initially shown in up to 80% of patients after NSAID therapy [34]. The incidence of more serious GI complications is approximately 1–2% per year [35]. Unwanted effects in the lower GI tract (bleeding, perforation or strictures) are rarer [36]. Approximately 10–20% of NSAID-treated patients report dyspeptic complaints [37]; approximately 10% interrupt therapy within half a year because of these side effects. With continuous consumption of NSAIDs, 15–20% of the treated patients get an ulcer [35,36], and between 1% and 3% of continuously treated NSAID patients have to receive hospital treatment for GI bleeding or perforation. As a result of NSAID-induced gastric ulceration, bleeding or perforation, approximately 150 000 hospital days, at a cost of €64 million, are spent each year in just one nation (Germany) [38]. Adding the expenses for hospital treatment to the costs of the simultaneously prescribed gastroprotective drugs, the annual cost in Germany is approximately €128 million, purely for patients with legal health insurance [38]. In one study based on results from the large United States databank ARAMIS, the risk of a severe GI complication is increased 5.5-fold by therapy with NSAID [39]. At present it is estimated that in Germany up to 2000 patients per year bleed to death after NSAID therapy. However, this number is probably an underestimate because these results were derived only from patients with legal health insurance [38]. For comparison, 814 patients died in 1997 in Germany as the consequence of infection with HIV, or 1512 persons in motor accidents [40]. These data fit well with the conservative estimations from Great Britain with an estimated 12 000 hospital treatments and approximately 4000 deaths [41,42]. Estimations for the USA go from more than 70 000 hospital treatments and over 16 000 NSAID-induced deaths [43]. In this context, the conclusion published by A Herxheimer certainly rings true, that patients for whom NSAIDs are prescribed are not adequately informed about the symptoms of a possible GI complication (such as upper abdominal pain and tarry stools). When such complications occur, patients often fail to interrupt taking the medication in time, or they consult a physician too late [44].

Risk factors

Various studies have identified the following risk factors for NSAID-induced GI side effects that can in part be brought into the planning of prophylaxis: simultaneous corticosteroid therapy, earlier GI side effects, high dosage and long duration of NSAID therapy, advanced patient age, alcoholism, handicaps, and simultaneous anticoagulant therapy. When these risk factors are present, the indication

for NSAID therapy must be thoroughly scrutinized and, if appropriate, a prophylactic medication should be considered. First an attempt should be made, and not merely with older patients, to achieve the therapeutic goals with a minimally gastrotoxic analgesic, such as paracetamol, or to try a lower dose of NSAID. The use of COX-2-selective drugs such as rofecoxib and celecoxib also seems to be a safer option than using other NSAIDs in these risk groups. However, one limitation is that COX-2 might also have a role in healing ulcers of the stomach, and for this reason caution must be exercised in patients with a previous history of ulcer disease. It must also be emphasized that patients infected with *Helicobacter pylori* seem not to represent a risk group, and the eradication of *H. pylori* does not represent a safe form of prophylaxis [45].

Comparison of the GI side effects of different NSAIDs

The various NSAID substance groups induce GI side effects to widely varying extents. However, a basic problem in studying this is the comparability of the doses used. According to the results of various studies, one can presume that the ability of NSAIDs to induce GI side effects agrees with the following general ranking scheme: rofecoxib=celecoxib <ibuprofen <meloxicam <diclofenac-Na <naproxen <piroxicam <indomethacin <ketoprofen, in increasing order of activity [39,46–53]. However, at the low doses that this comparison is based on, ibuprofen displays primarily only analgesic effects. The results of several studies have also shown that meloxicam belongs to the less gastrotoxic NSAIDs. This applies especially for the low dose of 7.5 mg, which seems to have a similar effectiveness to 100 mg of diclofenac, or 20 mg of piroxicam [52,53]. In many cases, however, rheumatic patients require a higher dose; with increasing doses, gastrotoxic effects can start to appear more frequently [54]. This agrees with the fact that COX-2 selectivity decreases with higher doses of meloxicam [55].

Prophylaxis of an NSAID gastropathy

GI side effects of NSAIDs cannot be avoided when they are applied as a suppository or in intramuscular or intravenous formulations, because the inhibition of prostaglandin synthesis in the stomach proceeds primarily via the systemic route [56]. Several medication-related measures for preventing an NSAID gastropathy have been investigated in prospective studies. However, in comparing the study results one must observe the importance of the side effects. For patients, the subjective compatibility of the medication is the most important factor, but from a physician's point of view it is also important to prevent serious, and possibly even fatal, GI complications.

Antacids and H_2-receptor antagonists (eg ranitidine) are very effective at relieving subjective complaints, but they cannot prevent severe GI complications [35]. With the proton pump inhibitor omeprazole, in contrast, common GI complications can often be inhibited, although higher doses are not necessarily more effective. In addition, not only can the synthetic PGE_1 analogue misoprostol given prophylactically for between 4 and 6 weeks reduce asymptomatic lesions by 90% [57] but it can also reduce ulcer bleeding by 40%, as the MUCOSA study demonstrated [58]. However, the application of misoprostol often seems to be badly tolerated owing to the appearance of diarrhoea and abdominal pain: the discontinuation rate is high. An extensive cost–benefit analysis on the prophylaxis of NSAID gastropathy with misoprostol revealed that this form of prophylaxis can only be clearly recommended in high-risk patients [59]. Studies from different industrial countries show that almost a quarter of all patients aged between 60 and 65 years that received an NSAID also simultaneously received gastroprotective drugs such as H_2-receptor antagonists, proton pump inhibitors, misoprostol or antacids. In Great Britain the prescription rate of these drugs is approximately 20%, in Canada 25%, in France 34% and in Germany 28% [38,60]. In comparison with the use of COX-2 inhibitors the place of this strategy in therapy is difficult to predict and will possibly depend on price. As has always been the case, NSAID therapy, even with COX-2-selective inhibitors, should be discontinued with bleeding ulcers as a matter of principle. How long such a discontinuation should be done has not yet been investigated systematically.

Conclusion

The development of COX-2-selective inhibitors has already been praised with headlines such as 'super aspirin' or the 'drug of the next century', because the first clinical findings revealed the appearance of significantly fewer serious GI side effects. In comparison with other NSAIDs, a similarly strong analgesic and possibly also an anti-inflammatory effect can be achieved [46,47,49–51, 61–64]. However, the future might not look quite as satisfying as at first imagined, because it has become apparent that COX-2 does not simply have a significant role in pain and inflammation: it also has physiological functions in other organs. Furthermore, patient collectives in clinical studies are not always representative, because risk groups such as older patients or probands with chronic or GI conditions are normally excluded. In this way, side effects can appear in everyday life that are not observed in clinical studies. An excessive COX-2 selectivity, especially when the dose is increased, might also work disadvantageously. An important task for medical institutions will therefore be to report on the effectiveness and side-effect profile of COX-2 inhibitors in comparison with NSAIDs that have previously been used successfully, and especially in long-term studies. Overall, however, despite the theoretically imaginable side effects, the preliminary clinical findings are positive. Selective COX-2 inhibitors are without question an innovative pharmaceutical development that might have a considerable spectrum of use.

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