The Clinical Importance of Selective Inhibitors of COX-2 and New Antiinflammatory Agents Without Gastrointestinal Toxicity

SELEKTİF COX-2 İNHİBİTÖRLERİNİN KLİNİK ÖNEMİ VE GASTROİNTESTİNAL TOKSİSİTESİ OLMAYAN YENİ ANTİİNFLAMATUVAR AJANLAR

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Summary

Nonsteroidal antiinflammatory drugs (NSAIDs) are widely used as analgesic and antiinflammatory agents. But one of the limiting factors in the use of NSAIDs is the rather high incidence of gastrointestinal (GI) side effects which occur as a result of gastric prostaglandin inhibition. Cyclooxygenase (COX) is the principle enzyme in the production of prostaglandins and inhibition of COX is also the primary mechanism of actions of NSAIDs. Two isoforms of COX have been identified:COX-1and COX-2. The prostaglandins that play a vital role in gastric mucosal protection in the GI tract are derived from COX-1.

Recent studies with COX enzymes indicate that the antiinflammatory effects of NSAIDs relate to COX-2 inhibition, whereas the GI side effects relate to COX-1 inhibition. Essentially, currently available NSAIDs inhibit both COX-1 and COX-2. In order to reduce the GI side effects of NSAIDs, selective COX-2 inhibitors have been developed, which inhibit COX-2 isoform in inflammatory tissue but have only limited effect on COX-1 isoform in the stomach.

Key Words: Cyclooxygenase 1 and Cyclooxygenase 2 inhibitors, Prostaglandins, Gastrointestinal toxicity

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Özet

Nonsteroidal antiinflamatuvar ilaçlar (NSAİİ) analjezik ve antiinflamatuvar olarak yaygın kullanılan ilaçlardır. Ancak (NSAİİ)'lerin kullanımını kısıtlayan faktörlerden biri gastrik prostaglandin inhibisyonunun bir neticesi olarak ortaya çıkan oldukça yüksek gastrointestinal (GI) yan etki insidansıdır. Siklooksijenaz (COX) prostaglandinlerin oluşumunda temel enzimdir ve COX inhibisyonu, (NSAİİ)'lerin etkilerinin primer mekanizmasıdır. COX enziminin iki izoformu teşhis edilmiştir: COX-1 ve COX-2. GI bölgede COX-1'den oluşan prostaglandinler gastrik mukozal korumada hayati bir rol oynarlar.

Son zamanlarda COX enzimleriyle yapılan çalışmalar (NSAİİ)'lerin antiinflamatuvar etkilerinin COX-2 inhibisyonu ile ilişkili iken, GI yan etkilerinin COX-1 inhibisyonu ile ilişkili olduğunu göstermektedir. Esasen halen mevcut (NSAİİ)'ler hem COX-1 hem COX-2'yi inhibe ederler. (NSAİİ)'lerin GI yan etkilerini azaltmak için inflamasyonlu dokuda COX-2 izoformunu inhibe eden, fakat midede COX-1 izoformu üzerinde sadece sınırlı etkiye sahip selektif COX-2 inhibitörleri geliştirilmektedir.

Anahtar Kelimeler: Siklooksijenaz 1 ve Siklooksijenaz 2 inhibitörleri, Prostaglandinler, Gastrointestinal toksisite

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Nonsteroidal antiinflammatory drugs (NSAIDs) are among the most commonly used drugs worldwide. The major limitation to their use is their gastrointestinal (GI) side effects including the formation of gastric and duodenal ulcers. Chronic administration of NSAIDs causes ulcers in 10-25% of patients. There are two major components to the ulcerogenic effects of NSAIDs in the stomach, namely their topical irritant effects on the epithelium and their ability to suppress prostaglandin (PG) synthesis (1,2). Other topical irritant properties are predominantly observed with acidic NSAIDs. Aspirin

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is probably the best characterized NSAID in this regard. These properties may also be related to the ability of NSAIDs to decrease hydrophobicity of the mucus gel layer in the stomach, which has been suggested to be a primary barrier to damage induced by acid (3).

Prostaglandins are biosynthesized from the precursor fatty acid arachidonic acid. Cyclooxygenase (COX) is the key enzyme responsible for the production of PGs and first purified in 1976 and cloned in 1988. Recent studies have shown that there are two isoforms of COX: COX-1 and COX-2. These isoforms have similar activities in the formation of PGs. It has been proposed that COX-1 and COX-2 subserve different physiologic functions largely because of the striking differences in their expression and regulation. Inhibition of COX is also primary of action of NSAIDs (4-7).

COX-1 is a constitutive enzyme expressed in many tissues including gastric mucosa, kidney and platelet, and it is responsible for producing PGs involved in maintenance of essential physiological functions such as gastric mucosal integrity, renal function and platelet homeostasis. COX-1 is constitutively expressed in normal gastric mucosa. Gastroprotective effect of the PGs (Prostacyclin) produced in the gastric mucosa is well known and clinically important function and these PGs are derived primarily from COX-1. Evidence therefore suggests that the GI toxicity associated with NSAID use is primarily the result of inhibition of COX-1 and it displays the characteristics of a "housekeeping gene" in the stomach (8-13).

COX-2 is often referred to as the inducible isoform and normally is undetectable in most tissue or at least at very low levels. But its expression can be rapidly induced by proinflammatory stimuli, such as hormones, cytokines and endotoxins or mitogenic agents at sites of inflammation including inflammed GI mucosa (14). It is expressed in fibroblasts by stimulation of growth factor and in macrophages by liposaccharide and interleukin-1 in inflammation. PGs produced via COX-2 are believed to be major contributors to the inflammatory process. It has been thought to be responsible for pathological PG production at inflammatory sites and its inhibition is associated with an anti-inflammatory action (15-18).

The ability of an NSAID to cause gastric damage correlates well with the ability to suppress gastric PG synthesis. There is also a time and dose dependency of both suppression of gastric PG synthesis and ulcerogenic activity. Important roles for endogenous PGs have also been well documented in the stomach involvement in regulation of various functions such as mucosal blood flow, mucus secretion and bicarbonate secretion and in modulation of gastric mucosal integrity (19-21).

Currently available NSAIDs inhibit both COX-1 and COX-2 with little specifity. Many appear to inhibit one isoform to a greater extent than the other. Drugs that have the highest potency against COX-2 and more favorable COX-2 / COX-1 activity ratio will have potent antiinflammatory activity with fewer side-effects in the stomach than agents with a less favorable COX-2 / COX-1 activity ratio (10). The PGs that play such a vital role in maintaining mucosal integrity in the normal GI tract are derived primarily from COX-1. Thus it is the suppression of COX-1 activity by NSAIDs that is believed to be a crucial factor in the pathogenesis of NSAID gastropathy. Most data on selectivity of NSAIDs in COX inhibition have come from studies in animals or in isolated cells. No studies have compared the effects of various NSAIDs on the human GI mucosa (19). A study in animal model shows that COX-2 expression correlates with mucosal injury and inflammation and COX-1 expression is not being affected by injury. This suggest that increase in PG levels associated with gastric injury is related to the increase in COX-2 expression (22-23).

In order to reduce the GI side-effects of NSAIDs, selective COX-2 inhibitors have been developed which inhibit the COX-2 isoform in inflammatory tissue, but have only limited effect on the COX-1 isoform in the stomach. In contrast to nonselective COX inhibitors, selective COX-2 inhibitors lack gastric ulcerogenicity. Aspirin, and ibuprofen are much less active against COX-2 than against COX-1. These are the most potent inhibitors of COX-1 that cause the damage to the stomach (24-27). Traditional NSAIDs such as indomethacin and diclofenac nonselectively inhibit both COX-1 and COX-2 and produce GI lesions(1). There are at least two NSAIDs presently on the

market, nabumetone and etodolac, that show modest selectivity for COX-2.

The 100th year since the introduction of aspirin to the marketplace, the association of GI damage with the use of NSAIDs remains the major limitation to their use. So, numerous strategies have been used in recent years to develop new NSAIDs that spare the GI tract. The discovery COX-2 has stimulated several laboratories to develop selective inhibitors of this enzyme. One of these inhibitors celecoxib (SC-58635) is an effective analgesic in humans for moderate-to-severe pain following tooth extraction and is undergoing Phase II/Phase III clinical trials for arthritis and doesn't cause GI erosions. Celecoxib was recently shown to be a powerful inhibitor of colon carcinogenesis induced by azoxymethane in Fischer rats (18,28).

Meloxicam a new potent antiinflammatory drug with selectivity for COX-2, has already been registered in several countries worldwide for use in rheumatoid arthritis and osteoarthritis (29). The less marked ulcerogenic effect of Meloxicam may result from its preferential inhibition of COX-2 over COX-1. In some studies Meloxicam shows a greater degree of selective COX-2 inhibition compared to standart NSAID, although not as much as the highly selective compounds under development. In a study Meloxicam 7.5 mg had no effect on platelet aggregation or renal PGE_2 excretion when given to healthy volunteers. This outcome is related to the low level inhibition of COX-1 by meloxicam (30-34).

NS-398 is a selective COX-2 inhibitor. It is a potent anti-inflammatory agent but doesn't produce ty-pical GI side-effects (15). Development of selective COX-2 inhibitors, such as NS-398, opened a new era in which the side effects of gastric and renal lesions by NSAIDs could be ignored (29). In a comparative study of the effects of indomethacin and NS-398, to clarify the mechanisms of duodenal ulcerogenic activity of NSAIDs, indomethacin significantly decreases duodenal bicarbonat secretion and potentiates duodenal lesion in a dose-dependent manner, whereas NS-398 have no effect on these parameters (35-37). In a study, to examine the effect of NS-398 on the healing and repair process of gastric ulcers, daily administration of NS-398 beginning with the early stage of ulcer induction (days 1-5) caused significiant impairment of healing. In another study demonstrated that the gastric mucosa was ulcerated when animals were pretreated with indomethacin, a non-selective COX-1 and COX-2 inhibitor, but not when pretreated with NS-398 (3,8,9,19,25).

It has been reported that the selective COX-2 inhibitor L-745, 337 has a reduced liability for GI ulceration (2,38). It has also been shown to be 1000 fold more selectivity for COX-2 than for COX-1 in-vitro, with a good antiinflammatory profile in animal models (10,24,39).

MK-966 an analog of L-745, 337, is in Phase III clinical trials. It is highly selective COX-2 inhibitor (10).

Nimesulid, Flosulid and DUP-697 had been reported a few years ago to be potent antiinflammatory drugs that did not cause stomach ulcers or alter renal blood flow. It is now clear that they are selective inhibitors of COX-2 . Nimesulid is on sale over the counter in Italy, Portugal and Greece as an antiinflammatory analgesic, despite limited clinical profile. Nimesulid a preferential inhibitor of COX-2 and is almost as active as indomethacin and 10 times more active than ibuprofen (36, 37,40, 41). Flosulid (GCP- 28237). In a comperative study , to assess the GI tolerability of flosulide in man and compare with naproksen, flosulide have been found significantly better tolerated and causes less gastric mucosal damage than naproxen when given for two weeks (10, 26).

DFU, SC-58125, SC-58431, SC558 GCP-28238 are another highly selective COX-2 inhibitors and has gastroprotective effect (8,11,41-43).

Among the compounds that have been reported to show selectivity for COX-2, the rank order of potency against COX-1 is DUP-697> Celecoxib> Nimesulid-meloxicam-piroxicam-NS-398>SC-58125>flosulide>L-745, 337 with IC50 values ranging from 7 nM to 17 μM (43).

The gastric ulcer repair process both in man and in experimental ulcer models, is mediated by the secretion of growth factors, enzymes and extracellular matrix components (44). This repair process is delayed if gastric PGs are depleted. Some studies have shown that administration of ex-

ogenous PGs such as misoprostol, a stable analogue of prostaglandin E_2, can prevent the development or accelerate the healing of NSAID-induced gastric ulcers (45-48).

Some clinical studies indicated reduced toxicity for these NSAIDs may be attributable to the use of these agents at subtherapeutic doses. As yet, no clinically available NSAID has been shown to have significant in-vivo effects on COX-2 while sparing COX-1 activity in humans. However compounds that may be 100 to 300 fold more effective inhibitors of COX-2, but are not yet available for clinical use (20).

The identification of selective inhibitors of COX-2 will therefore lead to advances therapy.These potent and irreversible inhibitors of COX-2 can be designed that may provide a therapeutic equivalent for aspirin in inflammatory and proliferative diseases without deletorious effect on stomach mucosa,which limit aspirin's use in longtherm therapy (18,49). Aspirin is used in the prophylaxis of stroke and myocardial infarction attributable to the ability of this drug to irreversibly inhibit platelet thromboxane synthesis,have led to increase in its long therm use.It is typically used at much lover doses than are required for antiinflammatory or analgesic effects. However, even at these low doses (10-100 mg/day) aspirin can significantly increase the risk of GI bleeding and ulceration (3,18,49,50).

The role of two forms of COX in gastric mucosal lesions is not well understood. Less clear is why suppression of PG synthesis leads to gastric mucosal injury. Clearly further studies are necessary to assess whether NSAIDs specific for COX-2 enzyme,are nonulcerogenic and do not delay ulcer healing in humans at therapeutic doses.

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