Review

Cyclooxygenase-2 Inhibitors in Gynecologic Practice

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ABSTRACT

Treatment of pain and inflammation associated with dysmenorrhea, endometriosis, ovarian cancers and operative procedures is an ongoing challenge in gynecology. Understanding the roles of prostanooids and estrogen in these conditions and appropriate treatment approaches have advanced beyond traditional nonsteroidal anti-inflammatory drugs. In this article, the author describes some of the basic mechanisms of nonspecific nonsteroidal anti-inflammatory drugs and newer cyclooxygenase-2 inhibitors, especially as they are used in the obstetrics/gynecology practice.

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are often the first choice of treatment for acute myalgias, orthopedic injuries, post-operative pain, chronic rheumatoid arthritis, and osteoarthritis.¹ The newest class of NSAIDs, cyclooxygenase (COX) inhibitors, is being promoted heavily by the pharmaceutical industry. By the end of 1999, their first year on the market, sales in the United States skyrocketed to \$472 million for rofecoxib and \$1.4 billion for celecoxib. As newer NSAIDs and other alternatives become available, the practicing clinician needs to be fully aware of the therapeutic choices in specific applications. The purpose of this review is to provide a brief overview of COX-2 inhibitors that target the modulation of prostaglandin levels, especially in reference to gynecological applications.

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Prostaglandins

Prostaglandins are ubiquitous fatty-acid derivatives that serve as autocrine/paracrine mediators involved in inflammation and immune response modulation, renal function, vasomotor tone, platelet aggregation and blood clotting, differentiation of immune cells, wound healing, nerve growth, bone metabolism, ovulation and initiation of labor.

Tissue damage activates phospholipase A2, causing arachidonic acid to be cleaved from cell membrane phospholipids. Upon release, arachidonic acid can proceed down either the lipoxygenase pathway leading to the formation of leukotrienes and lipoxins, or the COX pathway leading to the formation of thromboxanes and prostaglandins.

Cyclooxygenase occurs in two isoforms, COX-1 and COX-2. COX-1 is present in most tissues, and maintains normal gastric mucosa and influences kidney and platelet function.¹ COX-2 is not present at baseline in most tissues. Exceptions include the central nervous system, the gastrointestinal tract, kidneys, bones, ovaries and uterus. COX-2 is inducible by pro-inflammatory cytokines and produces prostaglandins that mediate the inflammatory and pain responses.¹ Its inhibition is a therapeutic goal. COX-1 and COX-2 are products of two genes residing on different chromosomes. Both attach to different sites on arachidonic acid, but convert it to prostaglandins equally efficiently. Glucocorticoids inhibit the induction of COX-2, but do not affect COX-1 activity and baseline prostaglandins levels.

At sites of inflammation, transcription and *de novo* synthesis of COX-2 are triggered by exposure of inflammatory cells to endotoxin, interferon and cytokines. Hyperalgesic and pro-inflammatory prostaglandins are generated. In the stomach, COX-1 catalyzes the synthesis of prostaglandin E-2 (PGE-2) and prostaglandin I-2. These have cytoprotective actions and

help in maintaining gastroduodenal mucosa integrity. Inhibition of COX-1 enzymes reduces these cytoprotective effects, and can lead to gastric bleeding and ulceration.

Traditional NSAIDs

NSAIDs have been in use long before anything was known about their mechanism of action (table 1). Traditional NSAIDs inhibit both COX-1 and COX-2, and in so doing not only decrease inflammation and pain, but also promote gastrointestinal tract damage and bleeding. Inhibitory potency and selectivity of conventional first-generation NSAIDs for COX-1 and COX-2 vary greatly. However, at therapeutic concentrations none of the currently marketed NSAIDs spare gastric COX-1 activity.

Side effects of traditional NSAIDs

It is estimated that 25% of patients using NSAIDs experience some kind of side effect, with 5% developing serious health consequences (massive GI bleeds, acute renal failure, etc.). Trials have been pursued to identify which patients are at high risk for NSAID-associated gastrointestinal disorders. The occurrence of side effects varies with the NSAID. Racemic ibuprofen and dexibuprofen showed a 30% and diclofenac a 90% higher incidence of adverse drug reactions.² Proton pump inhibitors and NSAIDs have been co-administered in an attempt to improve gastrointestinal safety. Prolongation of wound healing can be worrisome as well. Acute renal failure can arise as a side effect of NSAID usage, especially in a subset of patients in a state of volume depletion.

The first-generation COX-2 inhibitors

Inhibitors specific for COX-2 should have less gastrointestinal toxicity than other less selective NSAIDs (table 2). Two medications that predominantly inhibit only COX-2, rofecoxib and celecoxib, are currently available by prescription in the United States.

Table 1. History of prostaglandin E pharmacotherapy.

Date	Breakthrough
Ancient times	Parts of the willow tree used to relieve pain and inflammation
1897	Acetylsalicylic acid isolated, identified and synthesized
1899	Bayer Company first marketed aspirin
1963	Indomethacin synthesized, followed by several other synthetic and semisynthetic NSAIDs
Mid-1970s	Investigations into development of aromatase inhibitors begins
1971	NSAIDs such as aspirin exert their actions primarily by inhibiting the production of prostaglandins
1976	COX enzyme purified
1984	COX enzyme shown to increase in inflamed tissue
1988	COX enzyme shown to be stimulated by interleukin-1
1988	COX enzyme cloned
1990	COX shown to be induced by endotoxin and prevented by glucocorticoids, but dexamethasone does not affect baseline prostaglandin formation, so postulated a second COX enzyme
1991	Second COX gene discovered and isoform cloned: COX-2
1999	Launch of COX-2 selective inhibitors: rofecoxib and celecoxib
2002	Second-generation COX-2 selective inhibitors: valdecoxib, parecoxib and etoricoxib

COX, cyclooxygenase

NSAID, nonsteroidal anti-inflammatory drugs

Table 2. Overview of cyclooxygenase modulating medications.

NSAIDS	Cyclooxygenase-2 inhibitors
I. Acidic	I. First generation
A. Carboxylic acids	A. Celecoxib
1. Fenamic acids	B. Rofecoxib
a) meclofenamate	II. Second generation
2. Acetic acids	A. Valdecoxib
a) sulindac	B. Etoricoxib
b) indomethacin	C. Parecoxib
c) tolmetin	
d) diclofenac	
e) ketorolac	
3. Pyranocarboxylic acids	
a) etodolac	
4. Propionic acids	
a) naproxen	
b) flurbiprofen	
c) ibuprofen	
d) ketoprofen	
5. Salicylic acids	
a) aspirin	
b) salsalate	
c) diflunisal	
B. Enolic acids	
1. Oxicams	
a) piroxicam	
II. Nonacidic	
A. Naphthylalkanones	
1. Nabumetone	

Celecoxib is 375 times more selective for COX-2 than COX-1, and does not inhibit COX-1 at therapeutic doses.¹ It is rapidly and completely absorbed following oral ingestion, even in the presence of food. Steady blood levels are achieved after 10 days. Celecoxib is metabolized by the liver to inactive metabolites that are excreted in the gut and urine. Its breakdown is slowed by fluconazole, which is metabolized by the same enzyme. It contains a sulfa molecule, so should be given with caution to patients with a history of sulfa allergy. In general, celecoxib is associated with a markedly lower rate of gastroduodenal injury, is safe and effective in the treatment of osteoarthritis, rheumatoid arthritis, and familial adenomatous polyposis, and results in the relief of acute pain and inflammation with less risk of renal toxicity. It is not recommended during the third trimester of pregnancy because it may cause congenital heart damage to the fetus.

Rofecoxib is completely absorbed when taken by mouth. Absorption is not influenced by food in the stomach. It is metabolized in the liver, but by a slightly different mechanism. It has been approved for primary dysmenorrhea, acute pain after dental and orthopedic surgery, fever, and pain and inflammation in osteoarthritis and rheumatoid arthritis.³ In clinical trials, gastrointestinal toxicity, including mucosal

damage, perforation, ulcers and bleeding, occurred significantly less often with rofecoxib than ibuprofen, naproxen or diclofenac.³ It does not affect bleeding time and platelet aggregation, but has no advantage in terms of renal toxicity.

The second-generation COX-2 inhibitors

Valdecoxib is a second-generation COX-2 inhibitor.⁴ It has improved potency and a broader therapeutic range than other COX-2 inhibitors, including celecoxib, and has a potential for once-daily dosing. It is the first, second-generation oral COX-2 specific inhibitor approved by the United States Federal Drug Administration for use in the treatment of dysmenorrhea, osteoarthritis and rheumatoid arthritis. In Europe, another second-generation COX-2 specific inhibitor, etoricoxib, is available. Due to the poor water solubility of valdecoxib, the prodrug, parecoxib, is being developed as an injectable valdecoxib for post-operative pain.⁴ In general, these second-generation COX-2 inhibitors exhibit improved gastrointestinal safety, are longer lasting, and are more effective at pain and inflammation control.

Side effects of COX-2 inhibitors

Several large, randomized, multicenter, placebo-controlled, double-blind trials have now confirmed that celecoxib is efficacious in pain relief (especially rheumatoid arthritis) while not affecting COX-1 activity in the gastrointestinal tract mucosa as evidenced by less frequent incidence of endoscopic ulcers compared with conventional NSAIDs.^{5,6} However, the most common side effect of both rofecoxib and celecoxib has been the development of dyspepsia with no correlation to gastric ulcers or blood loss.

Concern has been expressed that COX-2 inhibitors may increase the risk of cardiovascular thromboembolic events (myocardial infarction, stroke, cardiovascular deaths, and peripheral events, such as hypertension, edema and congestive heart failure) because of their inhibition of vascular prostacyclin synthesis and lack of an effect on platelet thromboxane A(2) production and aggregation. However, the Celecoxib Long-term Arthritis Safety Study, a large randomized trial comparing celecoxib to ibuprofen or diclofenac while correcting for prophylactic acetylsalicylic acid use, showed that there was no increased risk of serious cardiovascular thromboembolic events associated with celecoxib compared with conventional NSAIDs.⁷

There is an intrarenal expression of COX-2 within the macula densa of the kidney that increases with salt restriction.⁸ In COX-2 allele knockout mice, severe renal problems arise, especially in relation to the stimulation of renin expression caused by a low-salt diet.⁹ In a randomized, controlled trial in elderly persons receiving a low-salt diet, it has been shown that the effects of rofecoxib COX-2 inhibition on renal function were similar to those observed with nonselective NSAIDs (indomethacin).^{10,11} Others, however, have reported that COX-2 inhibition in healthy elderly subjects may spare renal hemodynamic function, although the effects on sodium excretion, as well as urinary prostaglandin E2 and 6-keto-prostaglandin F1 alpha excretion, appear to be

similar to those of nonspecific COX inhibitors, such as naproxen.¹² Other manifestations of sodium retention (such as pleural effusions) have been reported with the use of rofecoxib.¹³

In general, it is the consensus that COX-2 selective inhibitors, like other NSAIDs, must be used cautiously or not at all in patients with predisposing diseases such as chronic renal failure, severe cardiac disease, and hepatic failure.¹⁴

Dysmenorrhea

Primary dysmenorrhea is characterized by painful uterine contractility caused by a hypersecretion of endometrial prostaglandins.¹⁵ NSAIDs are the treatment of first choice. Many clinical trials (controlled and uncontrolled) have demonstrated the efficacy of NSAIDs, such as the fenamates (meclofenamate), arylacetic acid derivatives (bromfenac, diclofenac) and arylpropionic acid derivatives (naproxen, ibuprofen, ketoprofen) in relieving primary dysmenorrhea.¹⁶⁻¹⁹ Valdecoxib demonstrates analgesic efficacy for treating women with primary dysmenorrhea, based on onset, magnitude, and duration of analgesia similar to naproxen sodium.²⁰

Endometriosis

Endometriosis is a progressive, estrogen-dependent disease characterized by the extrauterine growth of endometrium-like tissue (endometrial glands and stroma) on the peritoneal surfaces of abdominal organs. Retrograde menstruation with subsequent attachment, invasion, and neovascularization is believed to give rise to the endometriotic lesions in women susceptible to attachment and growth of ectopic endometrial tissue.

Estrogen stimulates the growth of human endometrial tissue, and aromatase is key in its biosynthesis. Aromatase activity is not detectable in normal endometrium. Both an intact aromatase gene and the presence of aromatase enzyme activity are essential for growth of ectopic uterine tissue.²¹ Lack of aromatase expression in eutopic endometrium is maintained by binding of an inhibitory transcription factor to the aromatase promoter II. In endometriosis, an aberrantly expressed factor binds to this same promoter, activates aromatase expression, and thus local estrogen biosynthesis.²² The aberrantly expressed aromatase in endometriosis is stimulated by PGE-2, resulting in local production of estrogen that induces PGE-2 formation, thereby establishing a positive feedback cycle.²³ At the same time, deficient expression of 17- β -hydroxysteroid dehydrogenase type 2 impairs the inactivation of estradiol to estrone. Both favor accumulation of increased estradiol and PGE-2 in the endometrial tissues.

COX-2 is induced in the proliferative stage of the endometrium, and COX-2, rather than COX-1, is the primary isoenzyme involved in the endometrial productions of prostaglandins. Peritoneal PGE-2 in endometriotic stromal cells may also induce steroidogenic acute regulatory protein,

further contributing to the development of endometriosis.²⁴ Aromatase inhibitors have successfully treated unusually aggressive post-menopausal endometriosis,²³ and future treatment of endometriosis will likely combine both COX-2 and aromatase inhibitors. At the present time, however, dysmenorrhea, pelvic pain, and dyspareunia, rather than the disease itself, are currently the major indications for both medical and surgical therapies of endometriosis.²⁵

COX-2 in ovarian cancer

COX-2 is involved in critical steps of cancer onset and progression. It is highly inducible by tumor promoters and growth factors, overexpressed in cancer cells, and associated with enhanced proliferative activity, apoptosis inhibition, increased metastatic potential, and neoangiogenesis.²⁶

An increase in COX-2 expression may represent an independent prognostic factor associated with malignant transformation and tumorigenesis of epithelial ovarian neoplasms.²⁶ COX-2 expression is observed in 78.6% of ovarian cancers and 66.7% of borderline malignant tumors. It is significantly higher among cancers than benign cystadenomas. COX-2 expression may also mark sensitivity to platin-based chemotherapy in ovarian cancer in that COX-2, and not COX-1, is expressed in 80% of unresponsive cases, versus 35.7% of responsive patients.²⁶

Selective COX-2 inhibitors have yet to be tested for treating ovarian carcinoma patients. Acetylsalicylic acid, acetaminophen, and a COX-2 inhibitor (NS-398) decreased cell numbers and mitotic activity and increased apoptosis in human ovarian cancer cell lines *in vitro*.²⁷ With continuing progress in gene therapy, the COX-2 gene promoter region might function as a tumor-specific target for gene therapy of ovarian cancer.

Procedural analgesia

Preoperative administration of analgesics can prevent or reduce hyperalgesia and inhibit inflammation and pain by reducing the synthesis of prostaglandins in response to surgical injury. Neither celecoxib, nor rofecoxib, have an effect on platelets or bleeding time, so they need not be discontinued prior to elective surgery. Preoperative administration of parecoxib is well tolerated, safe and effective.²⁸

Postoperatively, propacetamol is well tolerated, and is as efficient against pain as ketorolac. Parecoxib sodium has been shown to be as effective as intravenous ketorolac, and superior to intravenous morphine in women experiencing moderate-to-severe pain after abdominal hysterectomy or myomectomy.²⁹

CONCLUSION

In regard to COX-2 inhibitors, concerns have been raised regarding costs versus benefits. NSAIDs such as diclofenac, naproxen and mefenamic acid have been on the market for over 20 years. They are economical compared with COX-2 inhibitors, so are likely to remain the drug of choice for patients at lesser risk.⁴ However, in obstetrics/gynecology

practice COX-2 inhibitors are likely to play evolving roles in treating abnormal uterine bleeding, endometriosis, ovarian cancer management and/or prevention, and perioperative pain, and thus deserve wider attention and application.

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