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The cardiovascular and gastrointestinal adverse effects of cyclooxygenase inhibitors seems to be a major concern that restricts their use in the treatment of urinary bladder dysfunction

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Flurbiprofen is a non-selective cyclooxygenase (COX) inhibitor, which inhibits the activity of both isoforms of COX (1 and 2). Also, flurbiprofen is one of the most potent non-steroidal anti-inflammatory agent (NSAIDs) in terms of prostaglandin inhibitory activity via reversible inhibition of COX, the enzyme responsible for the conversion of arachidonic acid to prostaglandin G2 (PGG2) and PGG2 to prostaglandin H2 (PGH2). COX exists as two isoforms, constitutive COX-1 and inducible COX-2. Prostaglandins (PGs) formed by COX-1 are primarily involved in the regulation of homeostatic functions in physiological processes, whereas PGs formed by COX-2 primarily mediate pain, inflammation, and cancer pathophysiology (e.g. prostate cancer) [1].

Aktas et al. [2] investigated the effectiveness and safety of flurbiprofen alone or in combination with alfuzosin, in the treatment of lower urinary tract symptoms suggestive of benign prostate obstruction (LUTS/BPO). The results showed that flurbiprofen increases the therapeutic effectiveness of alfuzosin by further improving symptoms in patients with LUTS/BPO. Combination therapy also improves urine flow compared to baseline. However, no superiority of monotherapy with flurbiprofen to alfuzosin is observed. Additionally, gastrointestinal adverse events are predominant in patients using flurbiprofen.

PGs contribute to urinary bladder physiology. It is known that PGs are released from the urinary bladder into the general circulation in response to distension. PGs originate from the urothelium and the muscle layer of the urinary bladder [3, 4]. PG synthesis is initiated by several factors, as follow: 1) detrusor muscle stretching, 2) urinary bladder autonomic nerve fibers stimulation, 3) urinary bladder mucosal damage, and 4) inflammatory mediators (e.g. due to neurogenic inflammation) [5]. Numerous studies describing the effects of PGs in the urinary bladder have been published. It was reported that exogenous PGs alter urinary bladder motor activity in *in vitro* and *in vivo* studies. A link between PGs and the muscarinic system has been described previously [6]. Nile et al. [7] observed, in animal models, that ATP can activate PGE2 production by a complex mechanism, involving the purinergic receptors P2X and P2Y. Moreover, the response was inhibited by indomethacin (a non-selective COX inhibitor) and decreased the cholinergically stimulated autonomous contractions in the isolated bladder. PGs seem to affect the normal activity of the parasympathetic branch of the autonomic nervous system of the urinary bladder. In patients with overactive bladder (OAB) a higher concentration of PGE2 was detected in urine [8]. Ikeda et al. [9] revealed that inflammation facilitates afferent nerve activity *via* EP1 receptors in animal models. The physiological effects of prostaglandin E2 via receptors EP1-EP4 were described. The stimulation of EP1 and EP3 receptors leads to contraction of urinary bladder smooth muscle cells, whereas the stimulation of EP2 and EP4 receptors causes muscle relaxation [10].

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The therapeutic effectiveness of flurbiprofen, which improved the lower urinary tract symptoms in patients with BPO, seems to be the result of modulation of urinary bladder activity. Given the aforementioned potential mechanisms of PGs action in lower urinary tract function, it appears that the non-steroidal anti-inflammatory drugs through modulation of PGs-dependent pathways mainly affect urinary bladder activity and not the urinary bladder outlet resistance associated with prostate enlargement. Thus, in relation to lower urinary tract symptoms when non-steroidal anti-inflammatory drugs are used in patients with LUTS/BPO, a significant reduction in the severity of irritative LUTS to a lesser extent of obstructive LUTS should be observed. It is well known that BPO may lead to detrustor overactivity (DO). Thus, the modulation of the EP1 and EP2 receptor activity (directly *via* EP1/EP2 antagonists or indirectly *via* COX inhibitors) could be a therapeutic goal in urinary bladder dysfunction such as OAB or in the case of DO due to bladder outlet obstruction in terms of benign prostate hyperplasia and enlargement (BPH/BPE).

However promising the observations that have been reported, the cardiovascular and gastrointestinal adverse effects of cyclooxygenase inhibitors seems to be a major concern that restricts their use in the treatment of urinary bladder dysfunction. Moreover, the influence of COX activity on renal function should not be forgotten. Therefore, urologists should know the main physiological effects of COX-1 and COX-2 and its clinical consequences. These effects are presented in Figure 1. The relationship between cardiovascular or gastrointestinal risk and different NSAIDs in dependence with cyclooxygenase selectivity is showed in Figure 2.

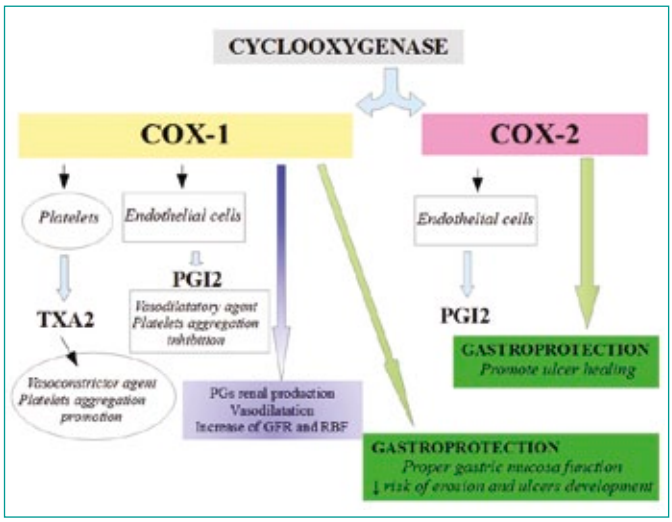

Figure 1. *The physiological effects of COX-1 and COX-2 activity.*

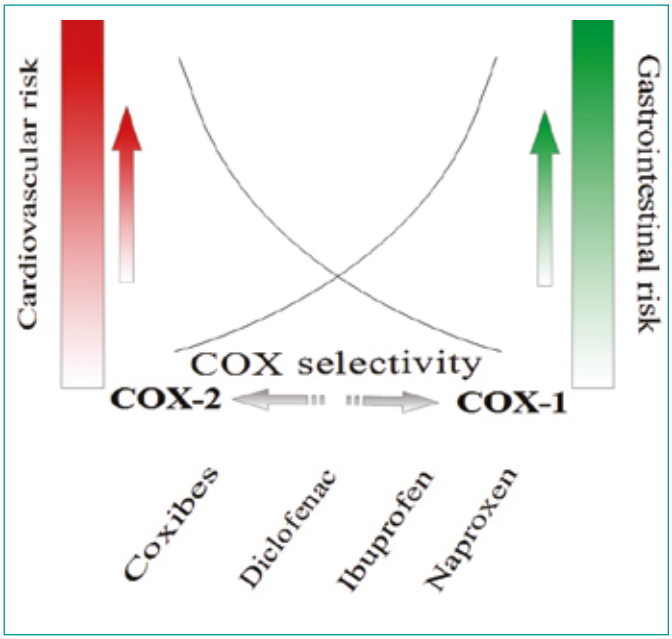

Figure 2. *The relationship between cardiovascular or gastrointestinal risk and different NSAIDs in dependence with cyclooxygenase selectivity.*

In the gastrointestinal tract, the maintenance of mucosal integrity is attributed exclusively to COX-1 without a contribution of COX-2 and ulcerogenic effects of NSAIDs are believed to be the consequence of inhibition of COX-1. The main function of COX-2 is the acceleration of ulcer healing. Therefore, both COX isoforms are essential enzymes in mucosal defence with specific contributions in various physiological and pathophysiological situations [11]. Endothelial cells are a source of prostacyclin (PGI2) and platelets are a source of tromboxane (TXA2). Platelets PGI2 production is mediated by COX-2 activity, thus COX-2 inhibitors suppress COX-2-dependent PGI2 synthesis. In physiology this sequence has mariginal influence on the antithrombotic balance due to the crucial role of COX-1 as a normal source of PGI2. In case of pathology when atherosclerosis occurs, the COX-2 starts to play a greater role as a source of PGI2. Moreover, more TXA2, as one of the most potent vasoconstrictor agents, is produced. Consequently, COX-2 inhibition has a more potent effect of prostanoid balance, favouring TXA2 production and promoting platelet-dependent thrombosis. COX-2 inhibition has been found to increase the risk of cardiovascular diseases even with short-term use [12, 13]. In the kidney, PGs regulate glomerular haemodynamics, glomerular filtration rate (GFR) and renal blood flow (RBF) by majorly affecting the calibre of afferent arterioles of glomeruli. NSAIDs

supress the renal production of PGs. Under normal conditions, this suppression does not affect the proper GFR and RBF. However, in the case of renal hypoperfusion (ischaemia) due to exaggerated vasoconstriction of renal vessels or local reduction of vasodilator PGI2 synthesis (e.g. caused by hypovolemia, postoperative pain, chronic kidney disease, obstructive uropathy, etc.), NSAIDs may exert deleterious effects on renal function.

When considering NSAIDs therapy in the "urological" patient, everyone should consider the comorbidities and risk of cardiovascular and gastrointestinal complications and appropriately choose the NSAIDs according to its cyclooxygenase selectivity.

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