IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals
ISSN 2349-7203
HUMAN

Human Journals
Review Article
February 2021 Vol.:20, Issue:3

NSAIDs, Cox-2 Inhibitors and its Cardiovascular Risk- A Review

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ISSN 2349-7203
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Submitted: 03 January 2021
Revised: 23 January 2021
Accepted: 12 February 2021

Keywords: NSAIDs, Cox-2 inhibitors, Prostocyclins, Thromboxane, Cardiovascular complications

ABSTRACT

Nonsteroidal Anti-inflammatory drugs are commonly used to treat pain and inflammation by inhibiting the cyclooxygenase-1 and cyclooxygenase-2 enzyme. This review will provide an educational update on the cardiovascular adverse reactions due by Cox-2 inhibitors and its pharmacology. The Cox-2 inhibitors might have lower risk of gastrointestinal toxicity but have increased risk of cardiovascular events like increased blood pressure, congestive heart failure and thrombosis. Cox-2 inhibitors interrupt the balance between thromboxane and prostocyclins that results in cardiovascular complications. By blocking prostacyclin formation but leaving platelet-derived thromboxane A2 generation that increases the thrombotic risk. Increased incidence of cardiovascular complications drew attention to the potential toxicity of the Cox-2 NSAIDS.

INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) are the most widely prescribed medications in the world more than a century because of their efficacy in reducing pain and inflammation[1,2]. In addition to their anti-inflammatory property, NSAIDs also have antipyretic and analgesic effects. These medications inhibit cyclooxygenases (COXs) enzymes including COX-1 and COX-2, which are rate-limiting enzymes for prostaglandins synthesis[2]. They also have numerous serious, potentially life threatening adverse drug reactions (ADR), because large number of patients are exposed to NSAIDs, their adverse effects represent a serious health problem.

During therapy with NSAIDs, the patient having risk of gastrointestinal, renal toxicity, increase in arterial blood pressure (BP) and the risk of heart failure[3]. Patients with cardiovascular disease and who are taking NSAIDs, especially cyclooxygenase-2 (COX-2) selective agents, are at greater risk of having an MI, Ischemic cerebrovascular events, or any other active athlerosclerotic process[5].

Types of NSAIDS

Traditionally NSAIDs were classified based on their chemical derivatives like salicylic acid, acetic acid, enolic acid, anthranilic acid or propionic acid[6].

Later they are classified according to their mechanism of action which inhibit both cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2) enzymes are known as non-selective NSAIDS and the drug which targets only the COX-2 pathway are known as COX 2 selective NSAIDS[7].

TABLE NO. 1: CLASSIFICATION OF NSAIDS [8]

NON SELECTIVE NSAIDS	• Diclofenac • Diflunisal • Etodolac • Fenoprofen • Flurbiprofen • Ibuprofen • Indomethacin • Ketoprofen • Ketorolac • Mefenamic acid
COX 2 SELECTIVE NSAIDS	• Celecoxib • Rofecoxib • Valdecoxib

Mechanism of action

The main mechanism of action of NSAIDs is the inhibition of the cyclooxygenase enzyme (COX). There are two isoforms of cyclooxygenase enzyme, COX-1 is the predominant isoform constitutively expressed in the body, and it plays a role in maintaining gastrointestinal mucosa lining, kidney function, and platelet aggregation and COX-2 not constitutively expressed in the body, and instead, it inducibly expresses during an inflammatory response plays a significant role in maintaining renal blood flow[9,10,11].

Cyclooxygenase-2 enzyme is induced in response to prostaglandins, growth factors and cytokines. Endothelial cells, macrophages and vascular smooth muscle cells are the source and location of upregulated COX-2[9,12,13]. It converts the arachidonic acid into thromboxanes, prostaglandins, and prostacyclins[14].

Pharmacology of COX -2

COX-2 selective inhibitors limit the endothelial cell synthesis of prostacyclin (PGI2) and arachidonic acid product that prevent the effects of thromboxane[15]. So increased cardiovascular risk associated with COX-2 inhibitors leads to the imbalance between thromboxane, prostacyclin and prostanoids production[16,17].

The COX-2 enzyme is responsible for generation of prostacyclin in the endothelium, which inhibits platelet aggregation and has vasodilatory and anti-proliferative properties. Importantly, there is no COX-2 present in platelets, so inhibiting this enzyme has no effect on platelet aggregation [18].

Thromboxane A2 (TxA2) is formed by the action of thromboxane synthase in the platelet. It has potent vasoconstrictor activity, stimulates platelet aggregation, induces the action of vascular smooth muscle cells, and facilitates cholesterol uptakes. Thromboxane A2 binds to a G-protein–coupled receptor on platelet membranes, induces a change in the integrin a2b3, which interferes the finals steps in platelet activation and results in platelet binding to fibrinogen and fibronectin. Contrarily, prostaglandin I2 (PGI2, or prostacyclin) causes vasodilation, inhibits vascular smooth muscle cell proliferation, reduces cholesterol uptakes and decreases platelet aggregation [16] and might have a role in cardioprotective vasculature in the context of ischemia-reperfusion injury [19].

Chronic Heart Failure and Hypertension:

The well-known side-effects of classical NSAIDs, like increase of blood pressure and development or worsening of chronic heart failure (CHF), are attributable to sodium and water retention in particular. Coxibs share these effects, although with different specificity, thus putting elderly patients at increased risk for fluid retention, blood pressure increase, and/or exacerbation of heart failure. Indeed, rofecoxib, at higher doses in particular, increases blood pressure significantly compared with celecoxib or naproxen [20].

This confirms that selective COX-2 inhibition blocks PGI-2 formation without inhibiting platelet derived TXA2[21,22]. Thereby increasing, adhesion, aggregation and platelet activation with a resultant possibility for thrombosis and ischemic events[23].

CONCLUSION

Chronic use of cox-2 selective inhibitors has been associated with increased cardiovascular risk. It seems to be dose and possibly dosing interval dependent. Moreover, that risk may vary by a patient's individual baseline cardiovascular risk. So adequate monitoring for signs and symptoms of adverse effects with proper patient education is required to increase patient safety during NSAIDs therapy. So the duration of Cox-2 therapy should be limited and only the minimal effective dose should be used. Therefore, understanding the potential danger of

the use of cyclooxygenase-2 inhibitors in patients who have cardiovascular risk factors is essential.

REFERENCES

1. C K S Ong, P Lirk, C H Tan, R A Seymour. An evidence-based update on nonsteroidal anti-inflammatory drugs. Clinical medicine& Reasearch.2007; 5(1):19-34.
2. Supakanya Wongrakpanich, Amaraporn Wongrakpanich, Katie Melhado, Janani Rangaswami. A Comprehensive Review of Non-Steroidal Anti-Inflammatory Drug Use in the Elderly. Aging and Disease.2018;9(1):143-150.
3. Zoltanvarga, Syed Rafay Ali Sabzwari, Veronika V. Cardiovascular risk of Nonsteroidal anti-inflammatory drugs: An under- Recognised Public Health Issue.Cureus.2017;9(4):e114.
4. Bombardier C, Laine L, Reicin A, Shapiro D, Burgos-Vargas R, Davis B, Day R, Ferraz MB, Hawkey CJ, Hochberg MC, Kvien TK, Schnitzer TJ, VIGOR Study Group. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR Study Group. The New England journal of medicine. 2000;343(21): 1520–1528.
5. Laura A. Perry, Charles Mosler, Ashton Atkins, Megan Minehart. Cardiovascular Risk associated with NSAIDs and COX -2 Inhibitors.US Pharm. 2014;39(3):35-38.
6. Bindu, Samik, *et al.* "Non-steroidal anti-inflammatory drugs (NSAIDs) and organ damage: A current perspective. Biochemical pharmacology.2020; 180:114147.
7. Rajeshwary Ghosh, Azra Alajbegovic, Aldrin V. Gomes. NSAIDs and Cardiovascular Diseases: Role of Reactive Oxygen Species. Oxidative medicine and cellular longevity. 2015.
8. Ida Ghlichloo, Valerie Gerriets. Nonsteroidal anti-inflammatory Drugs (NSAIDS). Stat Pearls. 2020.
9. Vane JR, Bakhle YS, Botting RM. Cycooxygenases 1 and 2. Annual Review of Pharmacology and Toxicology. 1998;38:97–120.
10. Catella-Lawson F, Mc Adam B, Morrison BW, *et al.* Effects of specific inhibition of cyclooxygenase-2 on sodium balance, hemodynamics, and vasoactive eicosanoids. The Journal of Pharmacology and Experimental therapeutics.1999;289(2):735–41.
11. Chaiamnuay S, Allison JJ, Curtis JR. Risks versus benefits of cyclooxygenase-2-selective nonsteroidal antiinflammatory drugs. American Journal of Health-System pharmacy.2006;63 (19):1837-1851.
12. Belton O, Fitzgerald DJ. Cyclooxygenase isoforms and atherosclerosis. Expert Review in Molecular Medicine.2003;5(9):1–18.
13. Linton MF, Fazio S. Cyclooxygenase-2 and atherosclerosis. Current Opinion in Lipidology. 2002;13(5):497–504.
14. Vane JR. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. Nature: New Biology.1971;231(25):232-5.
15. Egil Fosslien. Cardiovascular complications of non-steroidal anti-inflammatory drugs. Annals of clinical and laboratory science. 2005;35(4):347-85.
16. FitzGerald GA, Patrono C. The coxibs, selective inhibitors of cyclooxygenase-2. The New England Journal of Medicine.2001; 345(6):433–442.
17. Fitzgerald GA. Coxibs and cardiovascular disease. The New England Journal of Medicne. 2004; 351:1709–1711.
18. Foegh M, Ramwell P. The eicosanoids: prostaglandins, thromboxanes, leukotrienes, and related compounds. In: Katzung BG, editor. Basic and Clinical Pharmacology. 9th ed. New York, NY: Lange Medical Books/McGraw-Hill; 2004.
19. Bolli R, Shinmura K, Tang XL, *et al.* Discovery of a new function of cyclooxygenase (COX)-2: COX-2 is a cardioprotective protein that alleviates ischemia/reperfusion injury and mediates the late phase of preconditioning. Cardiovascular Research.2002;55(3): 506–19.
20. Ray WA, Stein CM, Daugherty JR, Hall K, Arbogast PG, Griffin MR. COX-2 selective non-steroidal anti-inflammatory drugs and risk of serious coronary heart disease. Lancet 2002; 360(9339):1071–3.

21. McAdam BF, Catella-Lawson F, Mardini IA, *et al* Systemic biosynthesis of prostacyclin by cyclooxygenase (COX-2): the human pharmacology of a selective inhibitor of COX-2. Proceedings of the National Academy of Sciences of the United States of America.1999;96(1):272-277.
22. Catella-Lawson F, Crofford LJ. Cyclooxygenase inhibition and thrombogenicity. The American journal of Medicine.2001;110:28S–32S.
23. Cheng Y, Austin SC, Rocca B, *et al*. Role of prostacyclin in the cardiovascular response to thromboxane A2. Science. 2002;296(5567):539–541.