The Effect of Celecoxib on Kidney Function in Elderly People

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Abstract

Nonsteroidal anti-inflammatory drugs, or NSAIDs, are typically prescribed to relieve inflammation and pain. The first two selective cyclo-oxygenase-2 (COX-2) inhibitors were approved for commercialization by the US Food and Drug Administration (FDA) in December 1998 and May 1999, respectively. Part of the reason coxibs, or selective COX-2 inhibitors, were developed was the expectation that they would be less harmful than conventional NSAIDs. The potential harm that conventional NSAID use may cause to the kidneys is widely recognized. There is a remote possibility of serious kidney toxicity, nevertheless.

Aim: The purpose of this study is to evaluate how celecoxib affects renal function in the elderly.

Conclusion: As the primary treatment for pain and fever, NSAIDs decrease the inflammatory response triggered by COX enzymes, exposing individuals to dangerous and detrimental adverse consequences on the kidney.

Recommendations: Physicians should be informed that patients with normal or impaired renal function have been linked to substantial or potentially fatal renal failure while using celecoxib for a short period of time. Celecoxib should not be taken by patients who have severe renal disease.

Keywords: NSAIDs, celecoxib, kidney, renal, elderly people, old people.

Introduction

Nonsteroidal anti-inflammatory drugs, or NSAIDs, are typically prescribed to relieve inflammation and pain. Significant gastrointestinal adverse consequences, like ulcers, bleeding, and perforation, have been related to the traditional use of NSAIDs. Food and Drug Administration (FDA) in the US authorized the first two COX-2 inhibitors that are selectively available for sale, which were released in December 1998 and May 1999, respectively. Part of the reason coxibs, or selective COX-2 inhibitors, were developed was the expectation that they would be less harmful than conventional NSAIDs. The gastrointestinal tract is the organ most commonly affected by NSAID side effects, with the kidneys coming in second. NSAIDs have a number of detrimental effects on the kidneys, such as decreased renal perfusion, glomerular filtration rate, and potassium and salt excretion. oedema, raised blood pressure, and interstitial nephritis (Mihalek, 2021).

Celecoxib is changed into a carboxylic acid metabolite and an inactive alcohol metabolite by the liver's CYP2C9 enzyme. Further research is necessary to investigate the possible pharmacological interaction between celecoxib and other drugs taken at the same time, as this could exacerbate the drug's nephrotoxicity (Mihovilovic et al., 2011).

NSAIDs, or nonsteroidal anti-inflammatory drugs, are widely prescribed for the treatment of both acute and chronic pain and inflammatory conditions. Renal function may be negatively impacted by these drugs, among other side effects. Nonselective NSAIDs function by blocking COX-1 and COX-2, which has advantages but also raises the possibility of negative side effects by lessening the anti-inflammatory effects of prostaglandins (Cheng & Harris, 2005).

NSAID use has the potential to cause acute renal failure, abnormalities in fluid and electrolytes, and

other renal problems. If a patient has a dangerous basic circumstance, usually a concomitant disease, they are more likely to suffer these detrimental renal outcomes. In cases of acute kidney damage, this is particularly true. This condition is risky in patients with actual or effective depletion of circulatory volume. The presence of co-occurring illnesses, diabetes, and preexisting hypertension, especially in elderly patients, increases the likelihood of adverse renal outcomes. Since NSAIDs have no detrimental effects on glomerular filtration rate (GFR) among senior citizens without risk factors and with normal renal function, age is not a factor in the development of NSAID-associated renal impairment (HARRIS, 2000).

Aim of the study:

The purpose of this study is to evaluate how celecoxib affects renal function in the elderly.

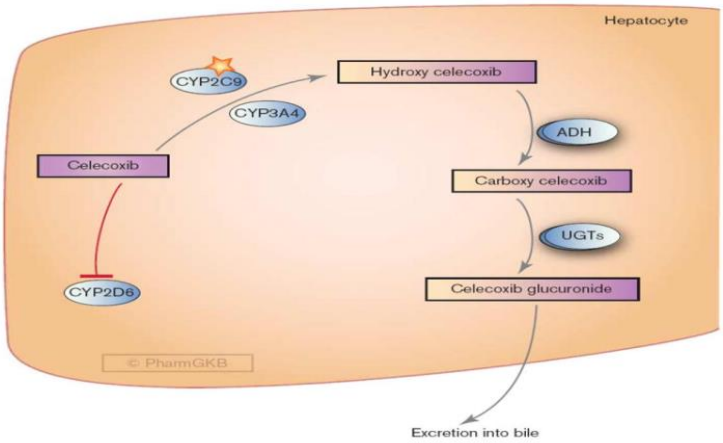
Literature review

Celecoxib pathways: pharmacokinetics and pharmacodynamics

Analgesic, antipyretic, and anti-inflammatory properties are possessed by NSAIDs, or nonsteroidal anti-inflammatory drugs, such celecoxib. authorized for the management of osteoarthritis, arthritis due to rheumatoid arthritis, a condition called ankylosing spondylitis, and acute discomfort. Celecoxib is administered to patients with familial adenomatous polyposis (FAP) as an adjuvant to surgery. a hereditary condition that raises the risk of colon cancer, and it also shows promise in the prevention of cancer. Prostaglandin (PG) synthesis is halted by the particular suppression of the PG G/H synthase 2 gene (PTGS2). celecoxib has anti-inflammatory and analgesic properties. PTGS1 and PTGS2, two PTGS isoforms, are sometimes called COX even though they also function as hydroperoxidase and cyclooxygenase (COX). For more details, see the Pharmacodynamics section (Grosser, 2006).

Celecoxib is one of the COX-2 selective inhibitors (pdCOX-2 inhibitors) that is the colloquial term for this subclass of NSAIDs, sometimes referred to as coxibs. The majority of tNSAIDs, or traditional NSAIDs, block both COX isoforms. Even yet, some were produced prior to the identification of COX-2, and their COX-2 selectivity is on par with celecoxib. In contrast to tNSAIDs that block both COX isoforms, pdCOX-2 inhibitors reduce the likelihood of serious gastrointestinal harm while also having anti-inflammatory properties (Lanas & Sopeña, 2009).

For many individuals suffering from severe arthritis or those who are sensitive to nonselective NSAIDs because of gastrointestinal side effects, PdCOX-2 inhibitors offer a substantial therapeutic advantage. Treatment management could be very beneficial for individuals who are at significant hazards for colorectal carcinoma or who require anti-inflammatory pain medication. It could also be important to measure the number of patients who benefit from celecoxib without experiencing any side effects. Knowing the pharmacogenomics of these pathways may help to improve the effectiveness and individualization of celecoxib medication (Grosser et al., 2006).



Hepatic metabolism of celecoxib: ADH, alcohol dehydrogenases; UGTs, UDP glucuronosyltransferases (Grosser et al., 2006).

Pharmacokinetics

Following oral therapy, celecoxib is readily absorbed and reaches maximum serum concentrations in about three hours. There is very little medication excreted intact (3%) since the liver metabolizes a large fraction of the medicine. The main excretions of celecoxib are urine and feces. Methyl hydroxylation is the primary metabolic pathway that changes celecoxib into hydroxycelecoxib. This process is mainly catalyzed by CYP2C9, with CYP3A4 accounting for just 25% of the total. ADH1 and ADH2, cytosolic alcohol dehydrogenases, further oxidize hydroxycelecoxib to carboxycelecoxib. 1-O-glucuronide is then produced when UDP-glucuronosyltransferase mixes carboxycelecoxib with glucuronic acid. According to Sandberg et al. (2002), none of the metabolites had any pharmacological effects. CYP2C9 polymorphisms are since CYP2C9 plays a major role in regulating celecoxib metabolism, it is anticipated to directly affect the pharmacokinetics of the drug and the variability of the drug response. Those with decreased CYP2C9 substrate metabolism, such as those with the CYP2C9*3 genotype, are more exposed to celecoxib than are those with normal CYP2C9 activity. Therefore, individuals using celecoxib and medications that suppress CYP2C9 should exercise caution (Metabolism, 2001).

Pharmacodynamics

By inhibiting the synthesis of certain inflammatory prostanoids (PGs), celecoxib has analgesic and anti-inflammatory properties. Prostanoids like PG and thromboxane are byproducts of lipid metabolic processes that arise from tissues-specific COX enzyme activity. In a multitude of biological processes, such as inflammation, pain, cancer, glaucoma, osteoporosis, cardiovascular diseases, and asthma, they act as physiological and pathological mediators. these compounds are significant players in these processes. Arachidonic acid (AA) is needed for the formation of prostanoids (PGs). The first stage of PG production is starting with either cytoplasmic (cPLA2, expressed by the PLA2G4A gene) or secreted (sPLA2, that are encoded by the PLA2G2A gene) PLA2, which is produced in response to an inflammatory or mitogenic signal that activates the cell membrane. When AA is liberated from Phospholipase, something happens (FitzGerald, 2004).

Prostanoids are produced as soon as AA is released by two isoenzymes, COX-1 (translated by PTGS1) and COX-2 (transcribed by PTGS2). As previously stated, this necessitates two sequential responses. AA is first changed into PGG2 by the initial COX reaction. The second reaction converts PGG2 into PGH2. After then, tissue-specific PG synthases change PGH2 into the active metabolites PGF2, PGD2, thromboxane (TA2), prostacyclin (PGI2), and PGE2. Through their binding to certain prostanoid G protein-coupled receptors, these active metabolites regulate a number of physiological processes, such as inflammation, fever, blood pressure regulation, coagulation, and gastrointestinal protection (Funk, 2001).

Antineoplastic actions of celecoxib

Selective COX-2 inhibitors, especially celecoxib, are being studied as possible chemopreventive and therapeutic drugs for cancer in tests on patients for a variety of cancers. When combined with surgery, nonselective NSAIDs like sulindac have been used to prevent colon cancer in patients with familial apoprotein syndrome (FAP). a genetic illness that frequently results in colon cancer, since the 1980s. Celecoxib has been shown in both FAP patients and those with spontaneous colorectal adenoma to significantly reduce the frequency of colorectal polyps. Celecoxib has demonstrated anticancer effects against existing invasive malignancies, including lung, colon, and prostate tumors, in both in vitro and in vivo investigations. Although the precise nature of its anticancer actions is unknown, they may include both COX-dependent and COX-independent mechanisms (Schönthal, 2006).

In vitro investigations using celecoxib reveal that although it regulates a variety of molecular events linked to tumors, Most COX-independent actions were only demonstrated to happen in vitro at supratherapeutic dosages and these have not yet been clearly placed into a framework that explains clinical reactions. The cellular expression of the cell cycle inhibiting agents p21 (encoded by the gene CDKN1A) and p27 (encoded by the gene CDKN1B), as shown by cell culture trials, is elevated in the presence of celecoxib-mediated suppression of cell cycle progression, whilst the expression of cyclins (encoded by the genes

CCNA1, CCNB1, and CCND1) is lowered. Celecoxib-treated human colon cancer cells also exhibit enhanced oncoprotein-catenin (encoded by gene CTNNB1) breakdown, which is associated with markedly reduced tumor growth cells (Maier et al., 2005).

The fact that these studies were conducted using in vitro methods dosages 10-100 times greater than human plasma levels represents another significant restriction. By suppressing antiapoptotic molecules such as caspases and CHOP (encoded by the gene DDIT3), proapoptotic molecules such PDK1 (encoded by the gene PDPK1) and its downstream target AKT1, celecoxib triggers apoptosis. Celecoxib's anticancer effects could possibly be impacted by its ability to suppress tumor cell invasion and angiogenesis. Celecoxib therapy suppressed matrix metalloproteinase 9 and decreased the synthesis of vascular endothelial growth factor in cancer tissues and cell lines (Peluffo et al., 2004).

The harmful effects of ibuprofen and celecoxib on the kidney and liver

Rats' serum levels of TSB, ALT, AST, and ALP were affected by NSAIDs:

According to Aziz et al. (2018), the celecoxib group's serum levels of AST, ALT, ALP, and TSB were significantly higher (p0.05) than those of the ibuprofen and control groups, whereas the ibuprofen group's levels of ALT and ALP were not significantly different (p>0.05).

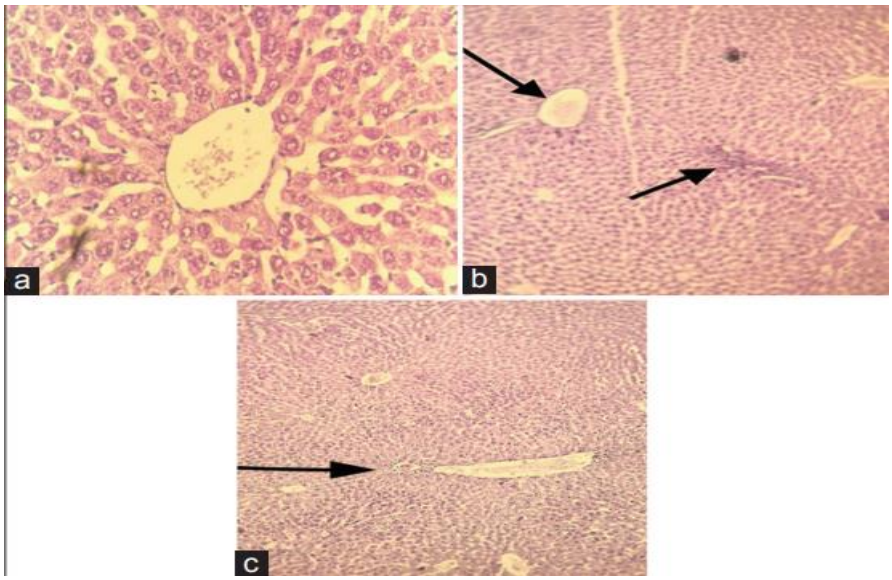
Rats' serum levels of creatinine and urea were affected by NSAIDs:

According to Aziz et al. (2018), there was a significant difference (p>0.05) in the serum levels of creatinine (0.69, 0.77, and 0.72) but not urea (29.66, 41.50, and 35.83) across the three groups, with the ibuprofen group having the highest level in comparison to the celecoxib and control groups.

Hepatic alterations

Histologically, there was some persistent portal inflammation and vascular congestion in the celecoxib group. as a result of liver alterations. Rats' serum levels showing notable alterations in biochemical markers further suggest that administering celecoxib at the recommended dosages may be hepatotoxic. These outcomes agree with those of a 2001 clinical trial of celecoxib conducted by Nachimuthu et al. (Nachimuthu et al., 2001).

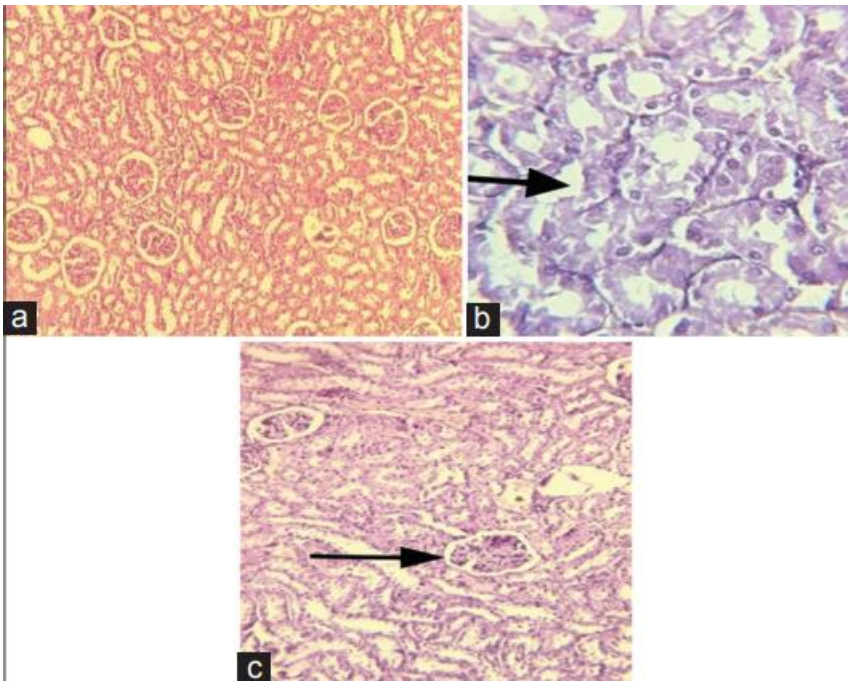
ALP, ALT, and AST levels are frequently employed as biochemical indicators of liver function. Changes in the liver's structure and function result in elevated blood levels of certain enzymes. These aminotransferases' (AST and ALT) elevated serum levels are a hallmark of all liver disorders. In fact, acute hepatitis can cause abnormally high levels of >1000 units (Vasudevan and Sreekumari, 2007)



Slices of liver tissue derived from both the treated and untreated populations. The liver histopathology of a typical rat control (400); rats treated with ibuprofen showed vascular congestion and anomalies in the portal tract; rats treated with celecoxib showed chronic vascular inflammation in the liver. (Aziz et al., 2018).

Kidney alterations

The kidneys in the ibuprofen group showed severe tubular necrosis and vascular congestion in the cortex and medulla. Conversely, the celecoxib group showed significant widespread vascular congestion that extended beyond the cortex. This outcome is in line with studies conducted by Rania et al. (2013), which shown that long-term high dosages of NSAIDs can cause glomerular alterations in the filtration barrier. Partial tubular necrosis and localized expansion of the mesangium of certain glomeruli (intraglomerular fibrosis) are seen. The glomerular basement membrane thinned, mesangial area increased, density reduced, and slit pores and foot processes enlarged as a result of celecoxib. But at the same dosage, ibuprofen causes severe necrotizing pyelonephritis, which is more dangerous than celecoxib (Hermann et al., 2005).



A portion of the kidneys' histological makeup in the groups that received treatment and those who did not. (A) Normal control rat kidney histology (400). (B) Rats given ibuprofen showed a histological alteration known as partial tubular necrosis. (C) A larger mesangium glomerular. alterations previously noted in rats receiving renal administration of celecoxib (Aziz et al., 2018).

Strong inhibitors of prostaglandin synthesis, nonsteroidal anti-inflammatory drugs (NSAIDs) Decrease renal blood flow, salt, free water, and glomerular filtration rate (GFR) dramatically in patients with ascites and cirrhosis. reduces excretion and the diuretic-induced natriuretic response. Because they can stop the cyclooxygenase (COX) enzyme from producing prostaglandins, NSAIDs offer therapeutic benefits. It has been suggested that celecoxib, a selective COX-2 inhibitor, is a more potent NSAID for treating inflammation than more conventional NSAIDs. Recent research has shown that in rats with cirrhosis and ascites, celecoxib has no negative effects on renal function (Guevara et al., 2004).

Acute interstitial nephritis (AIN) is one of the numerous significant causes of acute renal failure (ARF). This illness may be brought on by antibiotics, diuretics, anticonvulsants, nonsteroidal anti-inflammatory medicines (NSAIDs), and other medications. Clinical therapy has made use of cyclooxygenase 2 (COX-2) selective inhibitors.

Clinical therapy has made use of cyclooxygenase 2 (COX-2) selective inhibitors. to lessen the recognized gastrointestinal and renal toxicity of nonselective NSAIDs. While research on COX-2 inhibitor nephrotoxicity is still in its infancy, renal failure, both acute and chronic, edema, and imbalances in electrolytes are widely recognized as components of NSAID-associated nephrotoxic renal syndromes. Masu. At first, it was believed that NSAIDs' extensive organ damage resulted from their nonselective inhibition of cyclooxygenases. The kidneys, intestines, and other organs depend on two isoforms of cyclooxygenase 1 (COX-1); COX-2 is primarily thought to be activated in response to inflammation (Henao et al., 2002). The kidneys, intestines, and other organs depend on two isoforms of cyclooxygenase 1 (COX-1); COX-2 is primarily thought to be activated in response to inflammation (Henao et al., 2002). The renal medulla's interstitial cells express COX-2 in response to both hypertonic and water-deficient environments, and selective COX-2 inhibitors may make the kidney's medullary region more susceptible to cell death under these circumstances implies the existence of. Since all non-selective NSAIDs block his COX-2, salt accumulation is a common adverse effect. In light of this, COX-2-specific inhibitors might work just as well. When given orally once daily for four days to rats, when compared to a placebo, the anti-inflammatory drugs rofecoxib, celecoxib, diclofenac, and flurbiprofen dramatically decreased urine salt and potassium excretion. whereas meloxicam did not. NSAIDs given orally to rats for four days had short-term and time-dependent effects on urine electrolyte excretion, independent of COX-2-COX-1 selectivity (Harirforoosh & Jamali, 2005).

Discussion

Nonsteroidal anti-inflammatory drugs are most commonly recommended to stop the release of inflammatory mediators, which causes pain, fever, redness, and edema (NSAIDs). Cyclooxygenase (COX), an enzyme that catalyzes the transformation of arachidonic acid into prostacyclins, prostaglandins, and thromboxanes, is inhibited by NSAIDs as part of their mechanism of action. All three actions are counteracted by COX inhibition. There are two known isoforms of COX: Cox-1 and Cox-2. All tissues normally contain the "COX-1" isoenzyme, which when stimulated produces "PGs," which are vital for maintaining the health of organ systems including the kidneys and the walls of the stomach. On the other hand, under normal physiological conditions, "COX-2" is never expressed in most tissues; instead, it is expressed in response to bodily damage that triggers the creation of prostaglandins (Maicheen et al., 2017).

The potential harm that conventional NSAID use may cause to the kidneys is widely recognized. There is a remote possibility of serious kidney toxicity, nevertheless. Nonetheless, according to Ahmad et al. (2002), up to 5% of persons who are exposed to NSAIDs may have adverse renal effects of some kind.

GFR and renal plasma flow significantly decreased following the first 400 mg of celecoxib, according to **BRATER's 2002** study, suggesting that in this non-rigorous situation, treatment with this medicine may nevertheless have an impact on renal function. The transient effect of celecoxib on GFR largely subsided after two hours (BRATER, 2002).

AKI risk was observed to be higher in all exposure groups by **Lafrance & Miller (2009),** however it was mostly seen in individuals who took multiple agents or alternated between them. The danger of the majority of NSAIDs marketed in the USA has been estimated, even the more COX-2 selective ones. The three most selective medications—meloxicam, rofecoxib, and celecoxib—have been linked to a higher chance of AKI (Lafrance & Miller, 2009).

According to **Alkhuja et al. (2002),** NSAIDs can affect renal function in a number of ways. The two main clinical effects are lower perfusion within the kidneys and less elimination of sodium. A significant enough decline in renal function may lead to acute renal failure. Perazella and Eras report that thirteen and sixteen days after starting celecoxib therapy, two patients with persistent longterm kidney impairment had excessive volume and reversible acute kidney damage. Urinary chemical analysis was not documented when celecoxib treatment was discontinued, and renal function returned to baseline. Those authors have identified the use of celecoxib for 13–16 days as a possible cause and risk factor for the emergence of acute renal failure (Alkhuja et al., 2002).

Conclusion

As the primary treatment for pain and fever, NSAIDs decrease the inflammatory response triggered by COX enzymes, exposing patients to dangerous and detrimental adverse consequences on the kidney.

Recommendations

1. Physicians should be informed that patients with normal or impaired renal function have been linked to substantial or potentially fatal renal failure while using celecoxib for a brief period of time.

2. Celecoxib should not be used to patients who have severe renal disease.

3. As soon as treatment is initiated, kidney function should be routinely assessed for any signs of potential renal injury, especially in high-risk people.

4. Patients must be adequately informed by medical personnel about the warning signs and symptoms of severe renal toxicity.

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