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## NSAIDs and PPIs - REVIEW OF NEW REPORTS

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### Abstract

The aim of this study is to systematise knowledge on non-steroidal anti-inflammatory drugs (NSAIDs) - cyclooxygenase (COX) enzyme inhibitors and proton pump inhibitors (PPIs) inhibiting potassium hydrogen ATPase. A review of recent reports on possible side effects and new therapeutic options will be presented.

Results: Over the last few years, reports of PPI side effects have been published: drug-induced thrombocytopenia, severe hypomagnesemia, hyponatremia or rhabdomyolysis. In the case of NSAIDs, ancillary therapeutic effects in the supportive therapy of multiple myeloma or in the reduction of adenoma formation in the colon stand out, but also cases of acute

kidney injury in children. On the basis of meta-analyses, attempts were made to demonstrate the effect of individual NSAIDs on the occurrence of cardiovascular complications, stroke or myocardial infarction

Conclusions: Despite the fact that the indicated preparations were admitted to the list of drugs several decades ago, still their pharmacological potential (on the example of NSAIDs, which can be successfully used even in complementary therapy) has not been fully exploited. The aforementioned reports on side effects must not be forgotten. It is possible that the examples presented in the review will raise awareness in order to use these drugs with greater respect, in accordance with the recommendations in the leaflet.

**Key words: Non-steroidal anti-inflammatory drugs (NSAIDs), proton pump inhibitors (PPIs)**

## **INTRODUCTION**

Non-steroidal anti-inflammatory drugs (NSAIDs) are commonly used over-the-counter (OTC) drugs sold in many countries, including Poland [1]. These drugs are cyclooxygenase (COX) inhibitors. Since this enzyme exists in two isoforms, constitutive COX-1 (responsible for physiological functions) and inducible COX-2 (involved in inflammation), COX inhibition explains both the therapeutic effects (COX-2 inhibition) and side effects (COX-1 inhibition) of these drugs. [2]

The activity of many NSAIDs has been studied in several test systems, showing that most of those sold have higher activity against COX-1 or are equivalent against both isoforms. The most clinically advanced is meloxicam, which consistently shows higher activity against COX-2 than COX-1 in several test systems [2].

Despite the widespread familiarity of these drugs, NSAIDs are fraught with paradoxes that pose significant challenges to the medical community. Although NSAIDs are among the oldest drugs, new formulations continue to enter the market. Some preparations are safe enough to be sold over-the-counter for use in infants with fever, while others are only

available as prescription drugs and are a major cause of iatrogenic reactions, hospitalisations and deaths [1].

In contrast, the use of proton pump inhibitors (PPIs) is one of the most effective treatments for gastroesophageal reflux disease (GERD). These drugs work by blocking hydrogen-potassium adenosine triphosphatase ( $H^+,K^+$ -ATPase) effectively against excessive hydrogen ions in gastric acid [3]. Targeting protein-protein interactions (PPIs) has recently been recognised as a novel therapeutic approach for several diseases. There is also no shortage of new reports on adverse effects caused by PPIs [4].

## **OBJECTIVES AND METHODS**

The aim of this study is to systematize the knowledge about proton pump inhibitors and non-steroidal anti-inflammatory drugs. A review of recent reports on possible side effects but also new therapeutic possibilities will be presented. In order to find the latest information, a review of scientific papers was performed using Google Scholar covering articles from 2016 to 2021. A dozen scientific papers covering the scope of the publication were selected. Older review papers were used to provide introductory information on the drug mechanism.

## **PPIs - NEW REPORTS OF SIDE EFFECTS**

Although PPIs are well tolerated, some concerns have been raised about the safety of these drugs.

Drug-induced thrombocytopenia associated with the use of PPIs has been reported several times in the literature, and its incidence in the general population for non-heparin products is less than 1%. This phenomenon can be traced in one patient in whom thrombocytopenia developed immediately after starting PPIs twice and resolved immediately after discontinuation. This strong association suggests a potential role for PPIs in causing this rare but serious side effect. Subsequent regeneration of the platelet population after withdrawal of proton pump inhibitor pharmacotherapy was sufficient to suggest PPI use as the cause of thrombocytopenia. The most sensible first step in the evaluation and diagnosis of drug-induced thrombocytopenia is to discontinue PPI and, consequently, search for a method to normalize the platelet count. Similar phenomena apply to the studies conducted by Watson et

al, Binnetoğlu et al. and Dotana et al. In all cases, platelet counts increased as early as one day after PPI withdrawal. [5,6,7,8]

Many studies suggest that the drugs described are also the cause of electrolyte changes in the body. For example, severe hypomagnesemia can potentially lead to severe cardiac arrhythmias, resulting in death. However, results regarding this relationship remain controversial. Studies spanning more than 10 years related to iatrogenic arrhythmias resulting from PPIs have focused primarily on patients who have used PPIs long-term. However, there is no clear data that short-term intake of these substances is associated with a decrease in serum magnesium concentration. [9,10]

An association between any newly initiated PPI treatment (except lansoprazole) and hospitalization for hyponatremia has also been suggested. SIADH is believed to be the major cause of PPI-induced hyponatremia. The case of a certain patient who came to the hospital for treatment of Bell's palsy should be recalled here. On admission, the patient was ordered basic laboratory tests, including electrolytes. Results were normal, including a serum Na level of 135 mEq/l. Oral corticosteroids and proton pump inhibitors in combination with oral valacyclovir were started. After a few days, the patient's consciousness deteriorated. Laboratory tests were ordered again and this time the serum Na level was 103 mEq/L. The final diagnosis indicated SIADH. PPI discontinuation significantly improved urine dilution capacity and simultaneously increased serum sodium concentrations. The phenomenon of restoration of normal electrolyte balance after cessation of PPI treatment indicates that the use of these drugs was responsible for the etiology of SIADH. [11]

However, it is worth noting that there is another cause of the observed picture - PPIs are the most common cause of drug-induced acute interstitial nephritis, thus the pathogenesis of hyponatremia in patients using the above-mentioned drugs may also be connected with renal function impairment. Muscle damage is another example of rare side effects associated with PPI use. It is worth citing the case of a 67-year-old man with reflux esophagitis. The man started treatment with ezomeprazole within the last 10 months and was accompanied by back and limb fatigue and muscle pain. In laboratory tests, elevated creatine kinase levels were observed and CK isoenzyme showed MM pattern. He was diagnosed with rhabdomyolysis, which was caused by esomeprazole. Discontinuation of the drug quickly relieved symptoms, and serum CK levels returned to normal within 16 days. PPI-induced rhabdomyolysis is a rare complication. [12]

There are also cases of patients in whom the mentioned drugs cause a similar reaction of the body in a shorter time; A 45-year-old man was given esomeprozole 40 mg intravenously for pain control due to persistent lower chest discomfort that began 10 hours earlier. Then, 12 hours later, he complained of sudden severe pain in the right buttock, where an area with swollen tender muscles of about 8 cm in diameter was visible. The enzymes creatine kinase and lactate dehydrogenase were elevated. Thus, it should be noted that intravenous doses of esomeprazole may result in rhabdomyolysis. [13]

On the gastrointestinal side, there are some rare but dangerous side effects that can be found in the epidemiological review on PPI use; Suggested association between PPIs and development of specific gastric polyps. Fundic gland polyps (FGP) are small polyps usually located in the body and fundus of the stomach. Long-term PPI use is associated with extensive lining cell hypertrophy-high serum gastrin levels cause profound acid suppression, which in turn causes lining cell enlargement. Taking PPIs for a year or more increases the risk of not only growing polyps, but also bleeding from them. PPI therapy longer than 1 year has been shown to be associated with a fourfold increased risk of developing FGP. The literature describes the case of a 37-year-old woman who presented to the hospital complaining of bloody vomiting and tarry stools. She had been taking 10 mg rabeprazole daily for the past year for gastroesophageal reflux disease (GERD). EGD examination revealed > 20 stalked polyps. reddish, hemorrhagic polyps in the body and at the bottom of the stomach. In the present case, EGD was repeated 9 months after PPI withdrawal, where a significant reduction in the number of gastric polyps was observed. [14]

Subsequent reports on the association between excessive chronic PPI use and the occurrence of gastric polyps explain this by the phenomenon of increased expression of aquaporin-4 in the water channel and KCNQ1 in the potassium channel in mucosal gland cells. A 44-year-old man presented to the hospital complaining of tarry stools and anemia. He reported heartburn symptoms lasting for 10 years, so he took 15 mg of lansoprazole once daily for that period. In this case, in a patient who used PPIs for a long time, we observed an expansion of the distribution of AQP4- and KCNQ1-positive cells toward the surface of the fundic glands and apoptotic bodies were detected between the fundic mucosal glands, suggesting drug-related mucosal changes and the pathogenesis of an FGP-type lesion. [15]

An uncommon side effect of a PPI drug is presented in the case of a 12-year-old girl with no psychiatric history, who after starting omeprazole treatment developed psychotic symptoms, including delusional imaginations. Omeprazole was immediately discontinued and replaced

with ranitidine, resulting in an equally immediate reduction in adverse symptoms, followed by complete remission. [16]

### **NSAIDs - NEW REPORTS**

NSAIDs are widely used medicines. They are well established in the treatment of rheumatoid diseases (rheumatoid arthritis, osteoarthritis, rheumatic fever, acute gout), they are drugs on the first step of the analgesic ladder, aspirin is used as an antiplatelet drug, and in neonatology they are administered to close persistent Botall's duct in premature babies. Considering the above-mentioned properties, further potential applications of NSAIDs are being explored. A review of the literature on this subject allows to make some suspicions about new therapeutic possibilities in the treatment of cancer, familial adenomatous polyposis of the large intestine, neurodegenerative diseases (Alzheimer's disease, Parkinson's disease) or depression. [17]

One randomised, long-term study demonstrated the effectiveness of acetylsalicylic acid at a dose of at least 300 mg daily for five years in the primary prevention of colorectal cancer. It found that acetylsalicylic acid intake did not correlate with a reduction in tumour size, but did result in a reduction in the number of adenomas, which had a preventive effect on the occurrence of colorectal cancer. [18]

There was also a preclinical study which concluded that meloxicam has the potential to be used as an adjunctive treatment to the standard treatment procedure for multiple myeloma. [19]

In contrast, another study conducted in a mouse model of cutaneous melanoma demonstrated the anti-metastatic properties of naproxen-HBTA, which could potentially be used in combination therapy for cutaneous melanoma. Metastatic features such as proliferation, migration, invasion and colony formation were evaluated. The study showed that naproxen-HBTA induced apoptosis, inhibited invasion and new foci formation. Its daily administration significantly inhibited melanoma growth and progression in mice. [20]

Cocoxibs used together with SSRIs have shown antidepressant effects both in some human studies and in animal models. Their action helps to prevent an increase in pro-inflammatory cytokines, thus leading to an increase in serotonin and other neurotransmitters, which has an antidepressant effect. [21]

Although this review focuses on the role of NSAIDs in cancer, the non-cancerous but serious side effects of NSAIDs should not be overlooked. In a meta-analysis evaluating the

cardiovascular safety of NSAIDs, 31 studies involving 116,429 patients were included. The cardiovascular risks of naproxen, ibuprofen, diclofenac, celecoxib, etoricoxib, rofecoxib and lumiracoxib were examined. It was found that the highest risk of myocardial infarction was associated with rofecoxib, followed by lumiracoxib. As for stroke, the highest risk was associated with ibuprofen, while diclofenac was associated with the second highest risk. On the other hand, two drugs were associated with the highest risk of death from cardiovascular causes: etoricoxib and diclofenac. [22]

One meta-analysis showed an association of increased risk of gastrointestinal complications with 16 different types of NSAIDs. The relative risk ranged from 2 to 4, with ketorolac and azapropazone showing the highest risk, while aceclofenac and celecoxib had the lowest risk. It was also observed that risk increased with increasing NSAID dose [23].

A much larger study by Misurac et al [24] [25] concluded that non-steroidal anti-inflammatory drugs are an important cause of acute kidney injury (AKI) in children [25]; 1015 children with AKI were identified. Twenty-one children had clinical, laboratory and radiological findings suggestive of NSAID-related acute renal tubular necrosis. Fifteen of the 20 children (75%) for whom data were available were receiving NSAIDs at the recommended dosage limits. The fact that young children with NSAID-related AKI may have increased disease severity leads to the conclusion that their dosage should be reduced as often as possible [24].

Drugs rather than infections are currently the main cause of acute tubulointerstitial nephropathy (TIN) in children [25]. NSAIDs can cause acute TIN in children. Systemic hypersensitivity symptoms such as fever, rash and eosinophilia are rare in NSAID-induced acute TIN. NSAID-induced TIN may be associated with minimal change in nephrotic syndrome (26). Long-term prescription of NSAIDs can lead to chronic interstitial nephritis, chronic renal failure ( 27 ) and cardiovascular disease ( 28 ) in adults.

## **CONCLUSIONS**

Although PPIs and NSAIDs were admitted to the list of drugs several decades ago their pharmacological potential has still not been fully exploited. Finding a use for these drugs may not only improve the effectiveness and comfort of treatment, but also significantly reduce the cost of the entire therapy. We do not exclude the possibility that other commonly

used OTC drugs may also show a satisfactory but as yet undiscovered therapeutic effect in less common diseases or may be successfully used in treatments.

The aforementioned reports on the side effects of PPIs and NSAIDs should not be forgotten, as we know more about new rare side effects based on recent reports, and we are able to group individual NSAIDs according to the risk of ischaemic stroke or cardiovascular complications.

It is possible that the combination of healthcare professionals' knowledge of the most common side effects of these drugs, together with information about newly discovered side effects, will help to raise patients' awareness of the need to use these drugs with greater respect, in line with the recommendations in the leaflet.

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