



The Incidence of Upper Gastrointestinal Complications of Non-steroidal Anti-inflammatory Drugs in Elderly Patients

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Abstract

The incidence of upper gastrointestinal (GI) complications of non-steroidal anti-inflammatory drugs remains the most common side effect. The objective of this study was to compare the incidence of upper gastrointestinal complications of Ibuprofen as non-selective non-steroidal anti-inflammatory drug (NSAID) to Celecoxib and Meloxicam as selective non-steroidal anti-inflammatory drugs. This study included 4 groups of subjects aging above 50 years old divided into control group including 10 healthy volunteers suffering from the symptom of dyspepsia and three test groups, each test group included 10 osteoarthritic or rheumatic patients receiving only one NSAIDs (Ibuprofen, Celecoxib or Meloxicam) from at least 1 month. There was a statistically highly significant difference between the studied groups regarding the incidence of dyspepsia (p-value=0.008) and regarding the incidence of gastritis (p-value=0.042). In group II, there was a statistically significant correlation between the duration of administration of Ibuprofen and the incidence of dyspepsia. Similarly, in group III, there was a statistically significant correlation between the duration of administration of Celecoxib and the incidence of dyspepsia. Controversial, in group IV, there was no statistically significant correlation between the duration of administration of Meloxicam and the incidence of dyspepsia or gastritis or ulcer. Incidence of gastrointestinal side effects was lower for Celecoxib than for Meloxicam than for Ibuprofen. The study concluded that Celecoxib was safer than Meloxicam than Ibuprofen on the upper gastrointestinal tract.

Key Words: Non-steroidal anti-inflammatory drugs, upper gastrointestinal tract

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Introduction

Non-steroidal anti-inflammatory drugs (NSAIDs) providing anti-inflammatory, anti-pyretic and analgesic properties. They are among the most common prescribed drugs worldwide [1]. They are commonly used for the treatment of the signs and symptoms of osteoarthritis (OA) and rheumatoid arthritis (RA) and other inflammatory diseases [1].

Their use as a first-line therapy for pain and inflammation is well accepted and recommended by World Health Organization (WHO). It is estimated that everyday 30 million people worldwide use NSAIDs for anti-inflammatory and analgesic effects [2].

Inhibition of the cyclooxygenase (COX) enzymes that catalyze the biosynthesis of prostaglandins (PGs) and arachidonic acid is the most important mechanism of the anti-inflammatory action of NSAIDs. PGs are mediators of inflammation. COX-1 being a constitutive enzyme plays a role in the protection of mucosa in the GI tract. On the contrary, COX-2 is an inducible enzyme that is up-regulated only in inflammatory conditions [3].

Consequently, this fact led to the development of selective COX-2 inhibitors. GI toxicity is one of the serious drawbacks of NSAIDs that is widely associated with traditional NSAIDs. The GI complications range from gastric pain, dyspepsia development and drug intolerance to clinically significant gastroduodenal ulcer complications; such as bleeding, obstruction and perforations [2].

Davenport [4] reported that the endoscopic study of Douthwaite and Lintott in 1938 was the first study documenting the ability of non-steroidal anti-inflammatory drugs (NSAIDs) to cause ulceration and bleeding in the upper gastrointestinal tract.

Inappropriately, the ulceration of the gastrointestinal tract of NSAIDs do not correlate well with pain at its incidence because the analgesic action of NSAIDs may mask that ulcer pain [5]. Understanding the method by which NSAIDs cause gastric damage has helped in the development of prophylactic agents that reduce their toxicity [6].

According to the 2009 guidelines from the American College of Gastroenterology, patients are classified as being at high, moderate, or low risk for NSAID gastrointestinal toxicity [7].

High-risk patients are those with a history of complicated peptic ulcer disease or multiple (at least two) risk factors; moderate-risk patients are those with one to two risk factors, i.e., age above 65 years, high-dose NSAID therapy, previous history of an uncomplicated ulcer,

concurrent use of aspirin (including low-dose), corticosteroids, or anticoagulants; and low-risk patients are those with no risk factors.

Assessment of individual patient risk (cardiovascular, renal, and gastrointestinal) is necessary before prescribing anti-inflammatory treatments. To minimize the NSAID-related risk, clinicians should choose a gastro-protective strategy. This may include co-prescribing a proton pump inhibitor with a traditional NSAID, using a COX-2 selective inhibitor with or without a proton pump inhibitor. COX-2 inhibitors have been demonstrated to reduce the risk of both upper and lower gastrointestinal events, while proton pump inhibitors would not be expected to protect against the latter [8].

It has been recommended that patients at low risk for gastroduodenal complications and without cardiovascular risk (i.e., not taking aspirin) are good candidates for NSAID monotherapy, whereas patients at high risk for GI events without cardiovascular risk require addition of misoprostol or a proton pump inhibitor, or discontinuation of NSAIDs and initiation of either a non-NSAID analgesic or a COX-2 inhibitor as monotherapy [9].

The aim of the present study was to determine and compare the incidence of upper gastrointestinal complications of Ibuprofen as non-selective non-steroidal anti-inflammatory drug to Celecoxib and Meloxicam as selective non-steroidal anti-inflammatory drugs with the inclusion of a control group as a baseline.

Subjects and Method

This study was conducted on 40 osteoarthritis or rheumatic patients classified into 2 groups as the following:

Group I (Control group): including 10 healthy volunteers suffering from dyspepsia symptom.

Group II: including 10 osteoarthritis and rheumatic patients receiving 800 - 1200 mg/day of Ibuprofen from at least one month.

Group III: including 10 osteoarthritis and rheumatic patients receiving 200-400 mg/day of Celecoxib from at least one month.

Group IV: including 10 osteoarthritis and rheumatic patients receiving 7.5-15 mg/day of Meloxicam from at least one month.

All subjects were subjected to careful medical history taking through the filling of a scientific report and to upper endoscopy called Olympus endoscopy to study the effect of these three drugs on the gastric mucosa.

Then, the endoscopic findings were classified into dyspepsia, gastritis and ulcer. Finally, these endoscopic findings were compared according to the percent of their incidence in order to rank the three non-steroidal anti-inflammatory drugs according to their gastrointestinal toxicity and safety.

Results

An ethical approval was obtained from the University of Beni Suef and all volunteers gave signed informed consent.

The selected subjects in the four groups were well matched on age, sex and practice, making this an appropriate environment to assess the effects of different non-steroidal anti-inflammatory drugs on risk of adverse upper gastrointestinal events.

A total of 10 (5 females) volunteers suffering from upper abdominal pain as group I representing control group and 30 (15 females) osteoarthritic or rheumatic patients classified into three groups representing test groups were included in the study. Each test group included 10 (5 females) osteoarthritic or rheumatic patients receiving one non-steroidal anti-inflammatory drug from at least 1 month.

Concerning test groups, group II (Ibuprofen group) included 10 osteoarthritic or rheumatic patients with age range from 50 to 75 years with a mean value 62 ± 9.17 years receiving Ibuprofen at daily dose of 800 to 1600 mg. While, group III (Celecoxib group) 10 osteoarthritic or rheumatic patients with age range from 52 to 70 years with a mean value 61.4 ± 6.77 years receiving Celecoxib at daily dose of 200 to 400 mg. Group IV (Meloxicam group) consisted of 10 osteoarthritic or rheumatic patients with age range from 53 to 80 years with a mean value 64.4 ± 8.78 years receiving Meloxicam at daily dose of 7.5 to 15 mg.

All the human subjects included in our study were subjected to upper endoscopy. In Control group; the volunteers were subjected to upper endoscopy because they were suffering from severe upper abdominal pain. The endoscopy conclusion is shown in Table (1).

In group II, There was a statistically significant correlation between the duration of administration of Ibuprofen and the incidence of dyspepsia, but there was no a statistically significant correlation between the duration of administration of Ibuprofen and the incidence

of gastritis or ulcer. Similarly, in group III, there was a statistically significant correlation between the duration of administration of Celecoxib the incidence of dyspepsia, but there was no statistically significant correlation between the duration of administration of Celecoxib and the incidence of gastritis or ulcer. On the other hand, in group IV, there was no statistically significant correlation between the duration of administration of Meloxicam and the incidence of dyspepsia or gastritis or ulcer as illustrated in Table (2).

Table 1. The endoscopy conclusion of the four groups.

Upper Endoscopy Conclusion	Group I (n=10)	Group II (n=10)	Group III (n=10)	Group IV (n=10)	p-value
Dyspepsia	10 (100%)	2 (20%)	4 (40%)	3 (30%)	0.008
Gastritis	0 (0%)	3 (30%)	4 (40%)	4 (40%)	0.042
Ulcer	0 (0%)	5 (50%)	2 (20%)	3 (30%)	0.333

p-value ≥ 0.05 (non significant), and *P value < 0.05 (significant).

Table 2. The results of the statistical study of the correlation between the duration of administration of NSAIDs and the conclusion of upper endoscopy

Conclusion of Upper Endoscopy	Duration of drug administration in months					
	Group II (n=10)		Group III (n=10)		Group IV (n=10)	
	r coef.	p-value	r coef.	p-value	r coef.	p-value
Dyspepsia	0.662-	0.037	0.836-	0.003	0.604-	0.064
Gastritis	0.604-	0.064	0.393	0.261	0.147	0.684
Ulcer	0.602	0.066	0.542	0.106	0.447	0.196

r Using Pearson coefficient of correlation, p value ≥ 0.05 (non significant), and *p-value < 0.05 (significant).

There was no statistically significant correlation between the age and the percent of incidence of dyspepsia or gastritis or ulcer in the three test studied groups.

Similarly, there was no statistically significant correlation between the daily dose of NSAID and the percent of incidence of dyspepsia or gastritis or ulcer in the three test studied groups.

Finally, there was no statistically significant correlation between the dose of NSAID per weight and the percent of incidence of dyspepsia or gastritis or ulcer in the three test studied groups.

Discussion

As previously mentioned, NSAIDs are very commonly prescribed drugs in the world for its analgesic and anti-inflammatory properties. Evidently, the most common side effect of NSAIDs use is gastrointestinal toxicity, which is the primary limiting factor for their use [10-11].

The NSAID-induced upper gastrointestinal injury results from both local effects and systemic prostaglandin inhibition effected by blocking cyclooxygenase-1[12]. Consequently, many efforts were made for discovering selective cox-2 inhibitors. The first COX-2 selective inhibitor, Celecoxib (Celebrex), approved by the FDA in 1998 based upon the results of five clinical trials involving more than 5000 patients with degenerative or rheumatoid arthritis, showed comparable analgesia and efficacy to nonselective NSAIDs and placebo with fewer clinical and endoscopic gastroduodenal ulcers [13].

On comparing Ibuprofen group with control group, there was a statistically significant difference between the two groups regarding the percent of incidence of ulcer (p -value=0.012). In contrast, Yuan YH et al concluded after reviewing randomized placebo-controlled trials of oral NSAIDs from 1975 to 2006, that the incidence of gastroduodenal ulcer in placebo arms has not changed significantly over the last three decades [14]. Similarly, Soyulu A et al reported the absence of that statistically significant difference [15].

There was strong correlation between the age and the incidence of ulcer in patients receiving Ibuprofen as reported by Soyulu A et al & Hernandez D [15-16]. But, our results provided that the incidence of ulcer not correlated to the age.

Moreover, our study found that there was no statistically significant correlation between the daily dose of Ibuprofen and the percent of incidence of ulcer. In the contrary, it has been

concluded that there was strong correlation between the daily dose of Ibuprofen and the incidence of ulcer [15-17].

The study presented here was in accordance with the study of Aalykke [18] who found that the incidence of dyspepsia as a gastro intestinal side effect was strongly correlated with the duration of administration of Ibuprofen.

During comparing Meloxicam with Ibuprofen regarding the percent of incidence of ulcer, our results were in the contrary to an observational cohort study by Degner F et al [19] who reported a statistically significant difference regarding the percent of incidence of ulcer between patients taking Meloxicam and those taking Ibuprofen ($p < 0.001$).

Meloxicam caused lower percent of incidence of ulcer than Ibuprofen despite of the absence of a statistically significant difference. This means that Meloxicam has a greater gastrointestinal safety than Ibuprofen [20-25].

Although, Becker JC et al [26] paid the attention to the fact that overall gastrointestinal toxicity seems to be reduced with Meloxicam as selective cox-2 inhibitor when compared with unselective NSAIDs. A study found that after having Meloxicam, 40% of the included patients had more severe impairment of gastric mucosa [27].

A subsequent study by Lanes et al comparing the gastrointestinal risk of patients being prescribed Meloxicam with the older and more commonly used ibuprofen reported that the use of Meloxicam appears to result in a significant reduction in the risk of clinically important upper gastrointestinal events, even in patients at risk of these events [28].

Similarly, it has been concluded that complicated gastrointestinal events occur more frequently with traditional NSAIDs than Meloxicam [29-32]. Moreover, Scheiman [33] provided that Meloxicam decrease risk of upper GI ulcers and ulcer complications in patients with and without ulcer risk factors. Finally, Lim [34] reported that it appears that selective cyclooxygenase-2 inhibitors (Coxibs) improved upper and lower gastrointestinal safety based on results of clinical trials. Selective Coxibs are still capable of triggering gastrointestinal adverse events which made them as an option in the strategy of the prevention of NSAID induced gastrointestinal complications.

The results of our study suggested that Celecoxib showed more increasing upper gastro-intestinal safety and tolerability compared to Ibuprofen and even to Meloxicam. Concerning this suggestion, Celecoxib as COX-2 inhibitor was initially introduced to provide

symptomatic pain relief in the inflammatory diseases along with reduced gastrointestinal risk [35-36].

In accordance to our results, Deeks et al [37] & Hippisley-Cox J et al [38] provided that Celecoxib has greater upper gastrointestinal safety as the incidence of ulcers and serious upper gastrointestinal events was 40-75% lower.

On comparing Celecoxib group and Ibuprofen group, our results were in accordance with two studies paying the attention to the absence of statistically significant difference between the two drugs regarding the percent of incidence of ulcer [26, 33].

In contrast, other studies found that there was statistically significant difference between the two groups regarding the percent of incidence of ulcer (p -value=0.05) [37, 39-40].

Considering the percent of incidence of dyspepsia as an upper gastrointestinal side effect of Celecoxib, we concluded that there was no statistically significant difference. Similarly, one study reported that the statistical difference the incidence of dyspepsia is the same in case of Celecoxib and Ibuprofen [41]. Controversial, Deeks et al [37] reported that there was a statistically significantly difference regarding the incidence of dyspepsia.

There are many risk factors for the incidence of these gastrointestinal side effects of Celecoxib. The age above 60 years old is one important risk factor. Additionally, the mechanism of age-related NSAID-induced GI toxicity remains unknown [42]. However, age associated decreases in surface hydrophobicity, prostaglandin levels and impaired healing may contribute to the deterioration of the barrier property of the mucosa.

Interestingly, Hacklesberger et al [43] observed an age related decrease in surface hydrophobicity in the antrum of the stomach, which is also the primary site of NSAID-induced ulcers.

In addition, many studies reported that Celecoxib had greater upper gastrointestinal safety than Ibuprofen [20, 29, 30, 32, 33, 39, 37, 44]. It has also been provided that Celecoxib decrease risk of upper GI ulcers and ulcer complications in patients with and without ulcer risk factors [34]. Moreover, it appears that selective cyclooxygenase-2 inhibitors (Coxibs) improved upper and lower GI safety based on results of clinical trials [34].

Similarly, Becker JC et al [26] reported that overall GI toxicity seems to be reduced with Celecoxib. In addition, one study reported the incidence of GI intolerability adverse effects was lower with Celecoxib than with ibuprofen [45]. So, Coxibs are clearly associated with

improved gastrointestinal safety compared to NSAIDs, but this benefit is reduced and may be lost completely with concurrent low-dose aspirin use [46-50]. Also, Moore RA, 2007 concluded that complicated gastrointestinal events occur more frequently with NSAIDs than Celecoxib. In contrast, other studies reported that most of the ulcer complications that occurred after 6 months of CLASS study were in users of Celecoxib [51-52].

Our results agreed with the documentation of the absence of statistically significant difference between Celecoxib and Placebo regarding the incidence of ulcer [53-54]. Furthermore, Simon et al [53] noticed that there was no statistically significant difference between Celecoxib and Placebo regarding the incidence of ulcer even at 4 times the recommended dose of Celecoxib.

But, comparing Celecoxib group with Control group regarding the incidence of dyspepsia, the results reported a statistically highly significant difference (p -value=0.004). In contrast, other studies reported that Celecoxib wasn't significantly different from placebo regarding the percent of incidence of dyspepsia [53, 55].

On comparing Celecoxib group with Meloxicam group, there was no statistically significant difference between Celecoxib group and Meloxicam group regarding the incidence of dyspepsia or gastritis or ulcer.

The results also revealed that the incidence of ulcer was 30% lower in patients receiving Celecoxib than in patients receiving Meloxicam.

Moreover, Shunji et al [56] documented that several studies have already shown that Celecoxib, as a selective COX-2 inhibitor, is used as a strategy for the prevention of gastrointestinal damage. Evidently, Peura [55] illustrated that greater upper gastrointestinal safety of Celecoxib than Ibuprofen owes to cyclooxygenase-1 (COX-1) inhibition which is responsible for significant morbidity and mortality.

The discrepancies in the results are due to the advanced age which has been consistently found to be a primary risk factor for adverse gastrointestinal events of selective and non-selective non-steroidal anti-inflammatory drugs [57-58].

Other risk factors that have been identified in multiple studies are higher doses of NSAIDs (including the use of two or more NSAIDs), a history of gastroduodenal ulcer or gastrointestinal bleeding, *Helicobacter pylori* infection, concomitant use of corticosteroids, serious coexisting conditions, smoking, alcohol consumption and concomitant use of anticoagulants. Additionally, Schlansky [59] paid the attention to the fact that cocaine use,

stress, cytomegalovirus (CMV) or herpes virus (HSV) infection, and concurrent non-aspirin antiplatelet agents, chemotherapeutic agents, or selective serotonin reuptake inhibitors (SSRIs) also impart increased risk for GI complications in NSAID users.

Conclusion

Ibuprofen has less upper gastrointestinal safety than Meloxicam than Celecoxib. Hence, Celecoxib is safer than Meloxicam which is safer than Ibuprofen on the upper gastrointestinal tract. At the end, this conclusion led us to the recommendation to avoid Ibuprofen in rheumatic or osteoarthritic patients who are at high risk for developing upper gastrointestinal complications.

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