

Original Research Article

Study of gastrointestinal toxicity of selective COX-2 inhibitors in comparison with conventional NSAIDs

Hima Bindu K.^{1*}, Venkat Rao G.²

¹Department of Pharmacology, Kakatiya Medical College, Warangal-506007, Telangana, India

²Retired Associate Professor, Department of Orthopaedics, Kakatiya Medical College, Warangal-506007, Telangana, India

Received: 15 October 2016

Accepted: 22 October 2016

*Correspondence:

Dr. K. Hima Bindu,

E-mail: hk.himabindu@gmail.com

Copyright: © the author(s), publisher and licensee Medip Academy. This is an open-access article distributed under the terms of the Creative Commons Attribution Non-Commercial License, which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

ABSTRACT

Background: Adverse gastrointestinal events are the commonest unwanted effects of the NSAIDs, and are believed to result mainly from the inhibition of gastric COX-1, which is responsible for the synthesis of prostaglandins that normally inhibit acid secretion and protect the mucosa. Previous studies report, that selective COX-2 inhibitors are safer when compared to non-selective cyclooxygenase inhibitors, regarding their adverse effects on gastrointestinal system. But, recent studies reveal, that gastrointestinal safety of these selective COX-2 inhibitors is not much better than that of conventional NSAIDs. In view of the wider usage of selective COX-2 inhibitors, the study has been taken up to report, whether selective COX-2 inhibitors have got any advantages over conventional NSAIDs or not, in regard to their gastrointestinal side effects.

Methods: Patients were divided into eight groups, fifteen patients of each. Each group was given one of the NSAIDs from the eight drugs those were selected for the study, for 15 days. In the selected group, along with the symptomatic assessment of gastric toxicity, both pre and post-treatment values of Hb% are estimated, tabulated & subjected to statistical analysis.

Results: Both the drugs, diclofenac & meloxicam have shown significant changes in the Hb% values ('p' value 0.02 each), whereas selective COX-2 inhibitors like nimesulide & celecoxib were no less in gastric toxicity, in comparison with diclofenac, on symptomatic assessment.

Conclusions: In our short-term study, selective COX-2 inhibitors did not show any advantage over non-selective NSAIDs regarding their gastrointestinal toxicity.

Keywords: Adverse drug reactions, Conventional NSAIDs, COX-2 inhibitors, Gastric toxicity

INTRODUCTION

Non-steroidal anti-inflammatory drugs presently are the most widely used drugs in medicine and their annual sales in the world are more than 6 billion dollars. Presently, more than 100 NSAIDs have been tested clinically and more than 50 are there in the world market. Nearly 35 million people are taking them on daily basis and FDA has ranked them the most frequent cause of adverse drug reactions.¹ The spectrum of adverse reactions is broad. The most frequent problems are

gastrointestinal, the most common being dyspepsia. Dyspepsia is a common symptom of gastrointestinal complications of NSAIDs use and is usually complained by about 10-12% of patients taking NSAIDs. Dyspepsia may lead to non-compliance with NSAID therapy in 5-15% of patients.²

Persistent dyspepsia is one of the most frequent side effects of NSAIDs and with few exceptions; it can be an indicator of onset of future gastrointestinal toxicity.¹ Apart from dyspepsia, NSAIDs may also be associated

with many other gastrointestinal problems, the development of gastritis, gastric or duodenal ulceration, hemorrhage or perforation, and other events that may lead to hospitalization or death. They may have adverse effects in all parts of the gastrointestinal tract, not only the stomach or duodenum, but; the esophagus, small intestine and colon also may be affected.³

Dyspeptic symptoms occur in up to 60% of patients taking NSAIDs and there is a poor correlation between symptoms and endoscopically proved lesions. Up to 50% of endoscopically confirmed ulcers associated with NSAIDs are asymptomatic.

Although endoscopic studies reveal that gastric or duodenal ulcers develop in 15-30% of patients who regularly take NSAIDs, the chief concern is clinically important gastro intestinal problems, such as bleeding, leading to anemia. It has been estimated that more than 1,00,000 patients are hospitalized and 16,500 die each year in the United states, as a result of NSAID related gastrointestinal events.⁴

Since NSAIDs remain the single most commonly used class of therapeutic agents in medical practice today, the high prevalence of gastric erosions is a major public health concern and moreover, no drug in this class can safely be exonerated from gastrointestinal toxicity. NSAID induced gastric erosions and ulcers are indeed now identified as a serious problem of public health. Moreover, since over half of ulcers and bleeds will be silent, this problem has tended to be underrated and inadequately responded to.^{5,6}

Estimates of the absolute risk vary from approximately two cases of NSAID induced serious upper gastrointestinal adverse effects per 10,000 person months of prescriptions to a seven fold increase in the risk of hospitalization in patients with rheumatoid arthritis. NSAIDs are the direct cause of 20-30% of all cases of complications of peptic ulcer disease.⁷

Patients using NSAIDs are more than five times more likely to be hospitalized for treatment related gastrointestinal problems than non-users and mortality among patients hospitalized for gastrointestinal bleeding is 5-10%. These potential life-threatening events are all the more menacing because they mainly occur without antecedent gastrointestinal warning symptoms.⁸

NSAIDs apparently produce gastro duodenal damage by two independent mechanisms, a direct local irritant effect and a systemic effect. Thus, enteric- coated tablets that do not release NSAID in the stomach produce less mucosal damage than normal preparations, although they still appear to be ulcerogenic (Hoftiezer et al; Jaszewski et al, Oddsson et al). Therefore, the potential risk of gastro-duodenal complications may be reduced by the use of short-term preoperative parenteral NSAID

treatment compared with oral NSAID treatment, but not altogether eliminated. Even short- term NSAID treatment (3-7 days) in volunteers leads to endoscopically detectable superficial gastro-duodenal mucosal lesions, but not to a clinically significant risk of severe complications. Long- term treatment with NSAIDs, may lead to complications in the small and large intestine, including erosions and strictures (Aabakken; Rooney and Bjarnason). However, these complications have not been observed clinically during short-term treatment (less than one week). There seems to be no clinically important differences in serious gastrointestinal side effects between various NSAIDs when used for short-term treatment.⁹

Previous studies report, that selective COX-2 inhibitors are safer when compared to non-selective cyclooxygenase inhibitors, regarding their adverse effects on the gastrointestinal tract. But, recent studies reveal, that gastrointestinal safety of these selective COX-2 inhibitors is not much better than that of conventional NSAIDs.

It is therefore, important to assess the gastrointestinal safety and side effects of newer COX-2 inhibitors. In view of the larger usage of this new group of drugs, the study has been taken up to report, whether selective COX-2 inhibitors have got any advantages over conventional NSAIDs or not, in regard to their gastrointestinal toxicity, especially when used for a routine short-term treatment; by analyzing few non-selective and selective groups of NSAIDs.

Aims and objectives

Aims and objectives of the study were to compare the gastric toxicity of non-selective NSAIDs with that of selective COX- 2 inhibitors.

METHODS

An interventional and prospective study was taken up with the approval of institutional ethical committee. All patients included in our study gave informed consent for their participation and the study was done at Mahatma Gandhi Memorial Hospital, Warangal, India.

Inclusion criteria

- Patients of above 30 years age; of either sex
- Osteoarthritis patients
- Rheumatoid arthritis patients
- Patients with fractures and dislocations

Exclusion criteria

- History of acid peptic disease
- History of bronchial asthma
- History of bleeding disorders

Table 1: Drugs used in the study and their doses.

Paracetamol	650 mg tid (about 2 gm per day)
Ibuprofen	400 mg tid (1200 mg per day)
Diclofenac	50 mg bd (100 mg per day)
Nimesulide	100 mg bd (200 mg per day)
Meloxicam	7.5 mg bd (15 mg per day)
Rofecoxib	25 mg bd (50 mg per day)
Celecoxib	100 mg bd (200 mg per day)
Valdecoxib	10 mg bd (20 mg per day)

Patients were divided into eight groups, fifteen patients of each. Each group was given one of the NSAIDs from the eight drugs those were selected for the study. In the selected group, prior to the administration of drug, Hb% estimation was done in all the patients, by using Cyan methemoglobin method & the values were recorded and tabulated.

The patients were advised to take the concerned NSAID, for a period of fifteen days, and they were not put on any antacid or H2- blocker or proton pump inhibitor. All the out patients were briefed, of the common toxicity of the concerned NSAID and they were advised to inform us soon after the onset of symptoms like nausea, vomiting, diarrhea, epigastric pain, heartburn, dyspepsia, facial and pedal edema, headache and tinnitus. Whenever the patient reported an adverse effect, he or she was advised to stop the treatment and it was taken as the primary end point of our study, for that particular patient. After the completion of treatment, Hb% estimation was repeated again and the values were recorded, tabulated and both the pre & post treatment values were subjected to statistical analysis with the help of paired 't' test.

The following side effects were noted down, if any, during the treatment period, in a proper case sheet proforma and tabulated, separately for each drug.

Gastric toxicity parameters

- Nausea
- Vomiting
- Abdominal pain
- Heartburn
- Dyspepsia
- Hematemesis
- Constipation
- Diarrhea

RESULTS

In our present short-term study, non-selective NSAIDs like ibuprofen and diclofenac were shown to be associated with risk of gastric toxicity, diclofenac being on the higher side; whereas, among the selective COX-2 inhibitors, nimesulide and celecoxib were shown to be associated with higher gastric toxicity and meloxicam, rofecoxib & valdecoxib, little on lesser side.

Diclofenac & meloxicam have also shown significant changes in the Hb% values.

Table 2: Gastric toxicity.

Name of the drug	No of patients affected with gastric toxicity
Paracetamol	0
Ibuprofen	1
Diclofenac	3*
Nimesulide	3*
Meloxicam	1
Rofecoxib	1
Celecoxib	2*
Valdecoxib	1

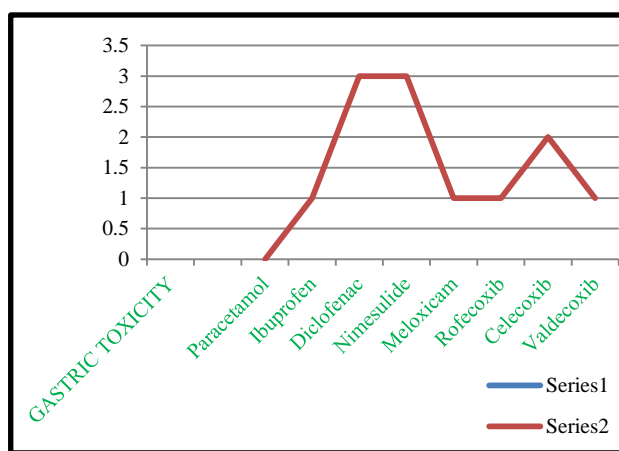


Figure 1: Graphical representation of gastric toxicity.

Table 3: 'p' value estimation for Hb% (in gm%).

Name of the drug	'p' value
Paracetamol	0.22
Ibuprofen	0.37
Diclofenac	0.02*
Nimesulide	0.12
Meloxicam	0.02*
Rofecoxib	0.20
Celecoxib	0.12
Valdecoxib	0.27

DISCUSSION

Effect on gastrointestinal system

In the present study, paracetamol proved to be extremely safe compared to other NSAIDs.² Ibuprofen showed little more, but not very bad gastric toxicity potential. This may be due to the fact that we use small doses of ibuprofen for its anti-inflammatory effect.¹⁰⁻¹² But, high dose ibuprofen was thought to be associated with increased gastric toxicity compared to other NSAIDs.¹⁰⁻¹³ Diclofenac was associated with gastric toxicity, higher than that of ibuprofen in our present study. The incidence of serious gastrointestinal adverse effects did not differ

between diclofenac and the COX-2-selective inhibitor, celecoxib (Juni et al, 2002), likely because diclofenac exhibits a degree of COX-2 selectivity that is similar to that of celecoxib. Nimesulide, also showed much gastric toxicity similar to that of non-selective NSAIDs; even though it has some COX-1 sparing action. This may be due to the fact that it is not a purely COX-2 selective inhibitor.^{1,14,15} Meloxicam has also been shown to have gastric toxicity, but, to a lesser extent than that of nimesulide.¹⁴

CLASS and VIGOR trials showed a lower relative risk of serious gastro intestinal complications with selective COX-2 inhibitors.¹⁶⁻²⁰ Furthermore, subsequent analysis of CLASS study, highlighted by FDA found that the benefits shown in six months analysis were not continued to the twelve months end point of study, placing doubt on the clinical significance of any gastro intestinal safety benefits from chronic use of selective COX-2 inhibitors over traditional NSAIDs.²¹ In the present study, celecoxib, a selective COX-2 inhibitor showed gastro intestinal toxicity similar to that of non-selective NSAIDs.^{15,22} FDA also found that, for upper gastro intestinal safety, there does not appear to be any meaningful advantage for celecoxib.²² But, the rate of gastro intestinal complication is less with rofecoxib and valdecoxib in the present short-term study.

In the present study, diclofenac and meloxicam have shown significant change in the 'p' value, in the assessment of Hb% change both before and after treatment, showing that there must have been gastric bleeding erosions which must have given rise to such changes and thus to anemia, without any alarming symptoms.

CONCLUSION

Inhibition of COX-1 by NSAIDs is linked to gastro intestinal toxicity. Those drugs, which selectively inhibit COX-2, were thought to have less gastro intestinal toxicity. But, they still had sufficient COX-1 inhibition to cause potent inhibitory effects on gastric PGE2 synthesis and thus are responsible for gastric toxicity, similar to that of non-selective NSAIDs. Hence, all currently used NSAIDs, including both conventional and selective COX-2 inhibitors do have inherent gastric toxicity, at therapeutic concentrations. Further long-term studies are required to assess the clinical safety of these selective COX-2 inhibitors.

Funding: No funding sources

Conflict of interest: None declared

Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. Dhikav V, Singh S, Anand KS. Newer non-steroidal anti-inflammatory drugs - A review of their

- therapeutic potential and adverse drug reactions. *JACM*. 2002;3(4):332-8.
2. Aggarwal KK. Paracetamol, An analgesic with excellent gastrointestinal tolerability. *Ind J Clin Pract*. 1999;10(2):69-72.
3. Russell R. Non-steroidal anti-inflammatory drugs and gastrointestinal damage- problems and solutions. *Postgraduate Med J*. 2001;77:82-8.
4. Bombardier C, Laine L, Reicin A, Shapiro D, Burgos-Vargas R, Davis B, et al. For the VIGOR Study group; comparison of upper gastrointestinal toxicity of ifofecoxib and naproxen in patients with rheumatoid arthritis. *New Eng J Med*. 2000;343(21):1520-8.
5. Fries JF, Miller SR, Spitz PW, Williams CA, Hubert HB, Bloch DA. Toward an epidemiology of gastropathy associated with non-steroidal anti-inflammatory drug use. *Gastroenterology*. 1989;96(2):647-55.
6. Roth SH. NSAID gastropathy - The central issue; *Drugs*. 1990;40(Suppl.5):25-8.
7. Brooks PM, Richard D. Non-Steroidal anti-inflammatory drugs - Differences and similarities; *New Eng J Med*. 1991;324(24):1716-24.
8. Steinfeld S, Poriau S. Patient and physician satisfaction with rofecoxib in osteoarthritis: Results of the EVA (Experience with VIOXX in Arthritis) survey. *CMRO*. 2001;17(2):81-7.
9. Kehlet H, Dahl JB. Are perioperative non-steroidal anti-inflammatory drugs ulcerogenic in the short term? *Drugs*. 1992;44(Suppl 5):38-41.
10. Riguez LAGR, Jick HS. Risk of upper gastro intestinal bleeding and perforation associated with individual non-steroidal anti-inflammatory drugs. *The Lancet*. 1994;343:769-72.
11. Griffin MR, Piper JM, Htery JRD, Snowden MRN, Ray WA. Non-steroidal anti-inflammatory {ory drug use and increased risk for peptic ulcer disease in elderly persons. *Ann Inter Med*. 1991;114(4):257-63.
12. Rampal P, Moore N, Van Ganse E, Le Parc JM, Wall R, Schneid H, et al. Gastrointestinal tolerability of ibuprofen compared with paracetamol and aspirin at over-the-counter doses. *J Inter Med Res*. 2002;30:301-8.
13. Henry D, Lim LLY, Rodriguez LAG, Gutthann SP, Carson JL, Griffin M, et al. Variability in risk of gastrointestinal complications with individual non-steroidal anti-inflammatory drugs; results of a collaborative meta-analysis. *British Med J*. 1996;312:1563-6.
14. Vainio H, Morgan G. Cyclo-oxygenase -2 and breast cancer prevention. *British Med J*. 1998;317:828.
15. Feldman M, Mahon AT. Do cyclooxygenase inhibitors provide benefits similar to those of traditional non-steroidal anti-inflammatory drugs, with less gastro intestinal toxicity? *Ann Inter Med*. 2000;132(2):134-43.

16. Deeks JJ, Smith LA, Bradley MD. Efficacy, tolerability, and upper gastrointestinal safety of celecoxib for treatment of (Steoarthritis and rheumatoid arthritis; systematic review of randomized controlled trials. *British Med J.* 2002;325:619-23.
17. Weckx LL, Ruiz JE, Duperly J, Mendizabal GA, Rausis MB, Piltcher SL, et al. Efficacy of celecoxib in treating symptoms of viral pharyngitis; a double-blind, randomized study of celecoxib versus diclofenac; *J Int Med Res.* 2002;30(2):185-94.
18. Boers M. NSAIDS and selective COX-2 inhibitors: competition between gastro protection and cardio protection; *The Lancet.* 2001;357:1222-3.
19. Emery P, Zeidler H, Kvien TK, Guslandi M, Naudin R, Stead H, et al. Celecoxib versus diclofenac in long-term management of rheumatoid arthritis; randomized double-blind comparison; *The Lancet.* 1999;354:2106-11.
20. Juni P, Rutjes AWS, Dieppe PA. Are selective COX-2 inhibitors superior to traditional non-steroidal anti-inflammatory drugs? ; *British Med J.* 2002;324:1287-8.
21. Cutts C, Lacaze A, Tett S. A Clinical audit of the prescribing of celecoxib and rofecoxib in Australian rural general practice. *British J Clin Pharmacol.* 2002;54:522-7.
22. Hrachovec JB, Mora M. Reporting of 6 - months VS 12-months data in a clinical trial of celecoxib; *JAMA.* 2001;286(19):2398.

Cite this article as: Bindu KH, Rao GV. Study of gastrointestinal toxicity of selective COX-2 inhibitors in comparison with conventional NSAIDs. *Int J Res Med Sci* 2016;4:5180-4.