J. Al Azhar University-Gaza 2003,Vol. 6, 2 P.47-56

# PHARMACOTHERAPEUTIC ANALYSIS OF NON-STEROIDAL ANTI-INFLAMMATORY DRUGS PRESCRIBED AT RHEUMATOLOGY / ORTHOPEDIC CLINICS.

**Waleed M. Sweileh**

An-Najah National University, College of Pharmacy,
Nablus, Palestine.

E-mail: *waleedsweileh@yahoo.com*

**Abstract:** *The objective of this study is to do a pharmotherapeutic analysis of NSAIDs prescriptions for patients attending rheumatology and orthopedic clinic. There were 326 prescriptions of NSAIDs for 307 patients (41.3% male, 48.6% female; 83.7% of patients were > 60 years old). The three most commonly prescribed NSAIDs were diclofenac (~40%), indomethacin (~30%) and naproxen (~28%). Duplication of oral/topical NSAIDs was found. Selective COX-2 inhibitors (coxibs) were found in ~ 18% of the prescriptions. Gastro protective agents were co- prescribed with NSAIDs in ~8% of the prescriptions that belong to 24 patients. Prescription database indicate that (1) patients are being treated with unnecessary multiple NSAID medications, (2) with high doses are being used in most cases and (3) finally gastroprotective co-therapy strategies are being under-utilized.*

## INTRODUCTION

Non-steroidal anti-inflammatory drugs (NSAIDs) exert their anti-inflammatory effects mainly through inhibition of the enzyme cyclo-oxygenase which catalyses the conversion of arachidonic acid to proinflammatory prostaglandins, particularly prostaglandin $E_2$. These play a major part in both experimental and clinical crystal induced inflammation, and act synergistically with other mediators (for example, bradykinin, leukotriene B4) to enhance capillary dilatation, pain sensitivity, and neutrophil chemotaxis (Terkeltaub R., 1999). Cyclo-oxygenase exists in two isoforms: cyclo-oxygenase-1 and cyclo-oxygenase-2. Conventional NSAIDs inhibit both cyclo-oxygenase-1 and cyclo-oxygenase-2 enzymes. Their anti-inflammatory effects are largely due to suppression of cyclo-oxygenase-2, and most adverse effects, particularly gastrointestinal toxicity, result from inhibition of

cyclo-oxygenase-1 (Feldman M, McMahon AT, 2000),( Jackson CG., 2001) The newer NSAIDs, such as celecoxib and rofecoxib are highly cyclooxygenase-2 selective [(4)]. Although both selective and standard NSAIDs inhibit cyclo-oxygenase-2 equally, the real advantage of selective cyclo-oxygenase-2 inhibitors, is that they are highly cyclo-oxygenase-1 sparing drugs, accounting for reduction in gastrointestinal toxicity by about 50% (Vane JR, Warner TD, 2000) . These drugs are generally well tolerated, and their clinical efficacy in patients with osteoarthritis or rheumatoid arthritis is comparable to that of non-selective NSAIDs (Riendeau D, Percival MD, Brideau C, Charleson S, Dube D, Ethier D, et al., 2001), (Vane JR, Warner TD, 2000) .

There is extensive amount of publications in the literature on the toxic and adverse effects of NSAIDs on gastrointestinal tract, renal system and other body organs (Bjorkman D., 1998 Nov. 2). However, these side effects could be minimized and avoided by the rational prescribing of this class of drugs. For example, it is rational to use low doses and to avoid prescribing several NSAIDS together. It is also rational to avoid non-selective NSAIDs in patients with peptic ulcer or gastrointestinal history or to administer mucosal protective or anti-secretory agent as a co-therapy with NSAIDs (Gabriel SE, Jaakkimainen L, Bombardier C., 1991), (Hawkey CJ., 1994), (Silverstone FE, Graham DY, Senior JR, Davies HW, Struthers BJ, Bittman RM, et al., 1996). Studies in other countries concluded that safer COX-2 inhibitors are cost/effective when reserved for patients at high risk of GIT complications (Hunt RH, Barkun AN, Baron D, Bombardier C, Bursey FR, Marshall JR, Morgan DG, Pare P, Thomson AB, Whittaker JS., 2000 Apr,16) . Finally, NSAIDs should be avoided, if possible, in elderly patients with congestive heart failure or hepatic or renal impairment who are taking other medications like oral anticoagulants or corticosteroids (Hogan DB, Campbell NR, Crutcher R, Jennett P, MacLeod N.,1994), (Sonnenblick EH, 2002 Oct;8)..

This article, is not aimed at discussing the current therapeutic guidelines for the treatment of rheumatoid arthritis or osteoarthritis. Rather, the purpose of this study is to analyze the rationality, both pharmacologically and economically of prescribed NSAIDs, the characteristics of NSAID users and the prescribing patterns of various types of NSAIDs at a charitable orthopedic and rheumatology clinics in northern Palestine area.

## METHODOLOGY

We collected three hundred and twenty six (326) prescriptions issued by an orthopedic/rheumatology clinic in a charitable medical center located in north Palestine. The prescriptions were traced and collected after being dispensed at the

pharmacy store. The prescriptions included in the study were only those containing at least one NSAID and is issued during the three month period of February, March and April 2002. This period of the year was chosen based on the number of patients attending the clinic during the year 2001 and found to be the most busy period of the year regarding the number of patients attending the clinic. Prescribed medications were entered into excel program for data analysis. Different trade names of the same drug were entered under the same generic name. Prices of drugs and total price of a prescription was calculated based on the full price present at the drug label. The prices were converted to the USD currency based on the currency exchange prices as of July 2002.

## RESULTS

Three hundred and twenty six (326) prescriptions that contain at least one NSAID were collected over three - month period (February – April 2002) from orthopedic/rheumatology clinics in northern Palestine. The characteristics of 307 patients receiving those prescriptions were shown in table one (table 1). Note that some patients were receiving more than one prescription.

Table (1): Characteristics of patients receiving the 326 NSAIDs containing prescriptions.

| Category | Number | Percentage |
|---|---|---|
| Gender | | |
| Males | 127 | 41.3% |
| Females | 180 | 58.6% |
| Age distribution | | |
| Males > 60 | 93 / 127 | 73% |
| Females > 60 | 144 / 180 | 80% |
| Total > 60 | 257 | 83.7% |

Females were attending the orthopedic / rheumatology clinics more than males and the majority of the patients were elderly. Actually, more than 80% of the sample patients were above 60 years old.

The average price in USD of the overall 326 prescriptions was 11.4 USD per prescription. The average price of COX-2 containing prescriptions was 12.7 USD per prescription.

The number of NSAIDs found in the 326 prescriptions were 532 agents with an average of 1.6 NSAID per prescription. Different dosage forms of the same type of NSAID were found in 19.7% of the prescriptions analyzed. The total number of medications in the 326 prescriptions were 1123 different agents (532 NSAIDs

plus 591 other non NSAID agents). The overall average of the number of medications per prescription was 3.4 per prescription.

Among all the NSAIDs, diclofenac sodium was ranking first followed by indomethacin, naproxen and ibuprofen. Diclofenac sodium tablet form was seen in 31 prescriptions, diclofenac sodium suppository form was seen in 42 prescriptions, Diclofenac sodium injection form was seen in 19 prescriptions and diclofenac topical emugel was seen in 37 prescriptions. Diclofenac sodium tablets were prescribed at doses seen in table three (table 3). High strength diclofenac sodium tablets were seen more often than low strength tablets. Furthermore, more than one type of dosage form of diclofenac sodium were seen in the same prescription. Similar results were found with Naproxen sodium where the high strength (100 mg tablets) were more commonly prescribed than the lower strength tablets (50 mg).

Table (2):: Frequencies of the various types of NSAIDs present in the Prescriptions analyzed.

| Drug | Number of prescriptions containing the drug (in tablet or suppository or topical or injectable form) | * Percentage of prescriptions containing the drug |
|---|---|---|
| Indomethacin | 97 | 29.7% |
| Diclofenac | 129 | 39.5% |
| Sulindac | 18 | 5.5% |
| Piroxicam | 42 | 8.5% |
| Ibuprofen | 51 | 12.8% |
| Phenylbutazone | 3 | 0.9% |
| Diflunisal | 3 | 0.9% |
| Etodolac | 5 | 1.5% |
| Naproxen | 92 | 28.2% |
| Ketoprofen | 17 | 5.2% |
| Nabumetone | 6 | 1.8% |
| Aspirin | 14 | 4.2% |
| Rofecoxib | 24 | 7.3% |
| Celecoxib | 31 | 9.5% |

· Note that the total exceeds 100% because some patients are receiving more than one type of NSAID in the same prescriptions which creates an overlap among the percentages.

Table (3):: Frequency and dosage strength of diclofenac sodium seen in the prescriptions analyzed.

| Diclofenac sodium Form | Strength | frequency |
|---|---|---|
| Diclofenac sodium tab | 100 mg<br>50 mg<br>25 mg | 25 / 31<br>6 / 31<br>none |
| Diclofenac sodium supp | 100 mg<br>75 mg<br>50 mg | 21/42<br>16 /42<br>5/42 |

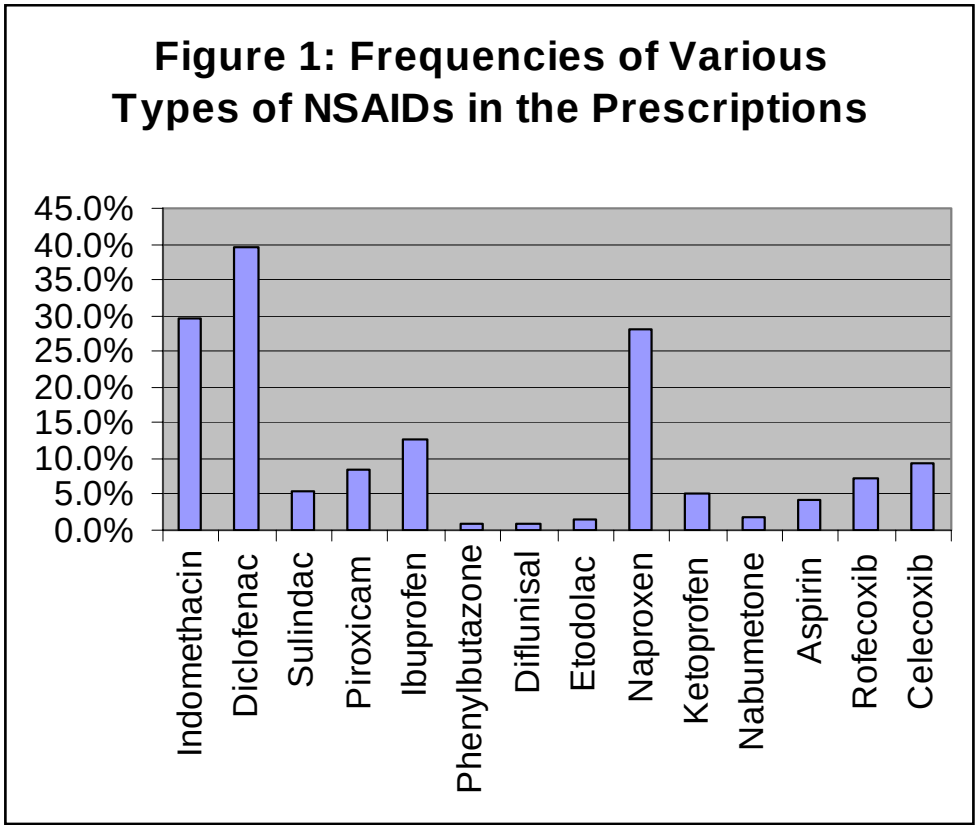



Figure (1): frequencies of Various types of NSAIDs in the prescriptions

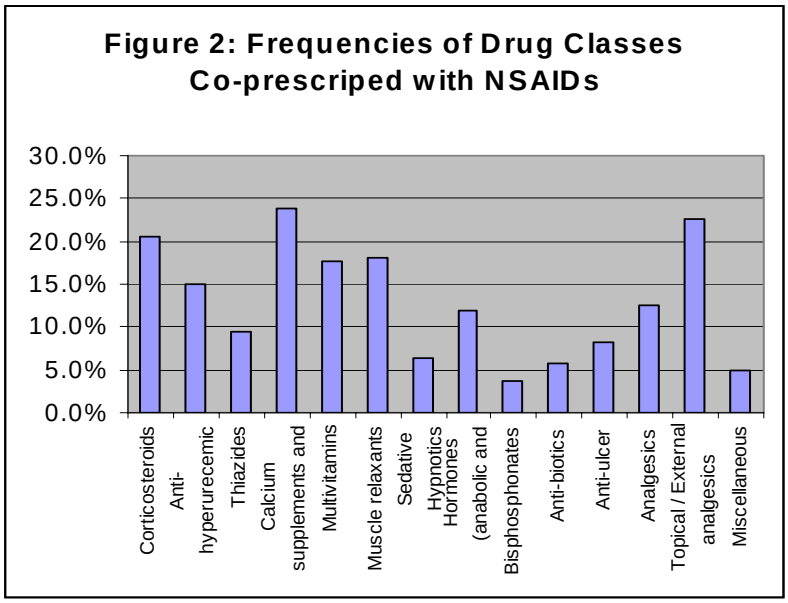
The other medications co-prescribed with NSAIDs were shown in table four (table 4) and include injectable and oral corticosteroids (in 67 prescriptions); anti-hyperurecemic agents (in 49 prescriptions); thiazide diuretics (31 prescriptions); calcium and vitamin D supplements (in 78 prescriptions); multivitamin (in 58 prescriptions); muscle relaxants (in 59 prescriptions); sedative hypnotics and anti-depressants (in 21 prescriptions); anabolic and estrogenic hormones (in 39 prescriptions); bisphosphonate drugs (in 12 prescriptions); antibiotics (in 19

prescriptions); anti-ulcer drugs (in 27 prescriptions that belong 24 patients); analgesics like acetaminophen, codeine or tramadol (in 41 prescriptions), topical / external analgesics (counterirritants) (in 74 prescriptions) and finally other miscellaneous agents (in 16 prescriptions). Some of these agents might be repeated more than once with different dosage forms in the same prescription like using antacids and H2 antagonists in the prescription with NSAIDs.

Table (4): Co-prescribed drugs / drug classes with NSAIDs

| | Co-prescribed drug/drug class with NSAIDs | Number of prescriptions containing that medication(s) | ** Percentage of prescriptions containing that medication(s) |
|---|---|---|---|
| 1 | Corticosteroids | 67 | 20.5% |
| 2 | Anti-hyperurecemic | 49 | 15% |
| 3 | Thiazides | 31 | 9.5% |
| 4 | Calcium supplements and Vit. D | 78 | 23.9% |
| 5 | Multivitamins | 58 | 17.7% |
| 6 | Muscle relaxants | 59 | 18.0% |
| 7 | Sedative Hypnotics | 21 | 6.4% |
| 8 | Hormones (anabolic and estrogen) | 39 | 11.9% |
| 9 | Bisphosphonates | 12 | 3.6% |
| 10 | Anti-biotics | 19 | 5.8% |
| 11 | Anti-ulcer | 27 | 8.2% |
| | Analgesics | 41 | 12.5% |
| 12 | Topical / External analgesics | 74 | 22.6% |
| 13 | Miscellaneous | 16 | 4.9% |

** Note that the total exceeds 100% because some patients are receiving more than one type of NSAID in the same prescriptions which creates an overlap among the percentages.




Figure(2): Frequencies of drug Classes Co-prescriped with NSAIDs

## DISCUSSION:

Non steroidal anti-inflammatory drugs (NSAIDs) are commonly prescribed in general medical practice and among rheumatologists for most commonly painful bone and dental disorders. For example, 70 million prescriptions for nonsteroidal anti-inflammatory drugs (NSAIDs) are dispensed in the United States, 20 million are dispensed in Great Britain, and 10 million are dispensed in Canada (National Totals for Prescriptions of Antiarthritic Drug Therapies in Canada. Montreal: IMS Canada; 1997). So far, no pharmaco-epidemiological studies on the use of NSAIDs have been carried out in Palestine which limits our knowledge on the extent of use of these drugs. However, unpublished data indicated that out of more than 9,000 prescriptions collected during the year 2001 from community pharmacies from the major districts in Palestine, 1879 prescriptions were containing one or more NSAID drugs mounting to a percentage of 20% of prescribed medications.

Factors contributing to the common use of NSAIDs are the availability of many NSAIDs as over-the –counter (OTC) preparations and the introduction of new cyclooxygenase-2 (COX-2) selective inhibitors. Despite our familiarity with these drugs, NSAIDs are full of paradoxes that pose significant challenges for the medical community. Rheumatologists face the choice of prescribing lower cost, mono versus combination NSAIDs, older NSAIDs versus the more expensive but

potentially safer NSAIDs and finally the choice of adding a gastro-protective agent as a co-therapy with NSAIDs.

The patients in our study who are receiving NSAIDs prescriptions mostly belong to a vulnerable elderly group who usually have multiple co-morbid conditions and are at high risk of developing drug related reactions and interactions. The majority of the patients receiving these NSAID prescriptions were females. This is expected since women at higher age become more susceptible to osteoporosis and other bone disorders that might require combinational therapy and that is why estrogen hormone, calcium, vitamin D as well as bisphosphonates were co-prescribed with NSAIDs. Analysis of the prescription database might suggest that those patients are being treated with unnecessary multiple NSAID medications. Even when they are prescribed a single type of NSAID like Diclofenac sodium, stronger doses are being used suggesting that there is a focus on immediate relief of rheumatoid arthritis or osteoarthritis pain while ignoring long term complications of these stronger NSAID doses. The combination of two or more different NSAIDs in the same prescription is of a questionable value. There is no evidence of synergism when two NSAIDs acting on the same enzyme are combined. Thus combining two NSAIDs may not improve the efficacy or potency of treatment. If at all, it only adds to the cost of therapy and more important, to the adverse effects. On the other hand, studies have shown that Diclofenac plus acetaminophen with or without codeine had superior analgesic effect compared with diclofenac sodium alone, acetaminophen alone , or acetaminophen plus codeine (Breivik EK, Barkvoll P, Skovlund E.,1999 Dec.).

Pharmacotherapeutic analysis of the NSAID prescriptions showed that the frequency of use of either of the two recommended gastroprotective strategies, involving either traditional NSAIDs combined with recommended anti-ulcer co-therapy or use of a selective cyclooxygenase 2-inhibiting drug (coxibs), was relatively uncommon. The percentage of coxib users was approximately 17% and the percentage of users of anti-ulcer / NSAID co-therapy was approximately 8%. This indicates that there is an underutilization of anti-ulcer co-therapy with NSAIDs in patients with high risk of developing drug-induced gastropathy. Analysis of the prescription database indicates that approximately a good percentage of the prescriptions contains corticosteroids mostly as methyprednisolone injections (Depo-Medrol®). This common use of corticosterids as an anti-inflammatory as a fast disease modifying antire-huematic drug (DMARD) increases the risk of NSAID induced gastropathy.

Pharmacoeconomic analysis of the prescriptions indicates that the average coxib prescription price is relatively close to the average price of the overall NSAID containing prescriptions. This suggests that price should not be a hindering factor

in prescribing the safer selective COX-2 inhibitors versus the less safe non-selective COX inhibitors.

As a conclusion, unnecessary multiple NSAID prescribing and poor therapeutic strategies of NSAID prescribing were sufficiently common to raise questions about the appropriateness of NSAID use among elderly patients attending orthopedic/rheumatology clinics. If these results reflect current medical practice in Palestine, then it might contribute to the incidence of avoidable gastrointestinal morbidity in elderly persons. Furthermore, it emphasize the need for strategies to reduce levels of NSAID prescribing.

## REFERENCES

Bjorkman D. Nonsteroidal anti-inflammatory drug-associated toxicity of the liver, lower gastrointestinal tract, and esophagus. Am J Med. 1998 Nov 2;105(5A):17S-21S. Review.

Breivik EK, Barkvoll P, Skovlund E. Combining diclofenac with acetaminophen or acetaminophen-codeine after oral surgery: a randomized, double-blind single-dose study. Clin Pharmacol Ther 1999 Dec;66(6):625-35

Feldman M, McMahon AT. Do cyclooxygenase-2 inhibitors provide benefits similar to those of traditional nonsteroidal anti-inflammatory drugs, with less gastrointestinal toxicity? *Ann Intern Med* 2000; 132: 134-143.

Gabriel SE, Jaakkimainen L, Bombardier C. Risk for serious gastrointestinal complications related to use of nonsteroidal anti-inflammatory drugs. A meta-analysis. Ann Intern Med. 1991;115:787-96.

Hawkey CJ. Healing and prevention of NSAID-induced peptic ulcers. Scand J Gastroenterol Suppl. 1994;29:42-7.

Hogan DB, Campbell NR, Crutcher R, Jennett P, MacLeod N. Prescription of nonsteroidal anti-inflammatory drugs for elderly people in Alberta. Can Med Assoc J. 1994;151:315-22.

Hunt RH, Barkun AN, Baron D, Bombardier C, Bursey FR, Marshall JR, Morgan DG, Pare P, Thomson AB, Whittaker JS. Recommendations for the appropriate use of anti-inflammatory drugs in the era of the coxibs: defining the role of gastroprotective agents. Can J Gastroenterol 2002 Apr;16(4):231-40

Jackson CG. Therapeutic potential of COX-2 inhibitors in arthritis. *Expert Opin Investig Drugs* 2001; 10: 1317-1325.

National Totals for Prescriptions of Antiarthritic Drug Therapies in Canada. Montreal: IMS Canada; 1997.

Riendeau D, Percival MD, Brideau C, Charleson S, Dube D, Ethier D, et al. Etoricoxib (MK-0663): preclinical profile and comparison with other agents

that selectively inhibit cyclooxygenase-2. *J Pharmacol Exp Therapeutics* 2001; 296: 558-566.

Silverstone FE, Graham DY, Senior JR, Davies HW, Struthers BJ, Bittman RM, et al. Misoprostol reduces serious gastrointestinal complications in patients with rheumatoid arthritis receiving nonsteroidal anti-inflammatory drugs. A randomized, double-blind, placebo-controlled trial. Ann Intern Med. 1996;123:241-9.

Sonnenblick EH.Cardiorenal differences among NSAIDs and coxibs: real-world experience. Am J Manag Care 2002 Oct;8(15 Suppl):S369-70.

Terkeltaub R. Pathogenesis of inflammatory manifestations caused by crystals. In: Smyth CJ, Holers VM, eds. *Gout, hyperuricemia, and other crystal-associated arthropathies.* New York: Marcel Dekker, 1999:1-14.