

# COX-2 Selective Nonsteroidal Anti-inflammatory Drugs : Current Status

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## Abstract

Since, their introduction, COX (cyclooxygenase enzyme)-2 specific inhibitors have become a rapidly growing segment of the prescription drug market. Researchers have recently focused on the potentially lethal side effects associated with their. FDA has banned the use of nimesulide (hepatotoxic) in pediatric patients and rofecoxib (cardiovascular complications) in both adults and children. COX-2 inhibitors may decrease vascular prostacyclin production and may tip the balance in favour of prothrombotic eicosanoids (thromboxane A<sub>2</sub>) and lead to increased cardiovascular thrombotic events. COX-2 inhibitors can also result into increase blood pressure, macular eruptions, urticaria, pseudoporphyria, erythema multiforme, oedema, worsening of heart failure, fatal allergic vasculitis and aggravation of doxorubicin-mediated cardiac injury. The COX-2 enzyme is also involved in the development of many organ systems, and its inhibition may lead to various congenital defects in neonates. It has been reported that COX-2 inhibitors also interfere with implantation, hence their use should be avoided in sexually active women at risk of pregnancy. However, presently the choice of COX-2 selective inhibitors for a particular patient should be based upon their relative efficacy, toxicity, concomitant drug use, concurrent disease states, hepatic and renal function and relative cost. ©

NSAIDs are the most commonly used over-the-counter drugs.<sup>1</sup> NSAIDs work by interfering with the cyclooxygenase pathway, which involves the conversion of arachidonic acid, by the enzyme cyclooxygenase(COX) to prostaglandins (PGs) in presence of an enzyme, cyclooxygenase(COX).<sup>1</sup> COX is available in two forms i.e. COX-1 and COX-2. The COX-1 enzyme is constitutive, and present in most tissues and controls normal body functions, such as stomach mucus production and kidney water excretion, as well as platelet formation.<sup>2</sup> In contrast, the COX-2 enzyme is induced dramatically by the action of macrophages, the scavenger cells of the immune system and is involved in producing prostaglandins for an inflammatory response.<sup>3</sup> As the attachment site of COX-1 is smaller than that of COX-2, so it accepts a narrower range of structures as substrates.<sup>3</sup> It is postulated that acetaminophen is more specific to a third form of cyclooxygenase, a 'COX-3', which exists in the brain, accounting for the drug's analgesic and antipyretic abilities.<sup>3</sup>

Researchers have recently focused on selective COX-2 inhibitors, which are believed to reduce inflammation

without influencing normal physiologic functions by inhibiting only COX-2. The first COX-2 selective NSAID approved by Food and Drug Administration (FDA) was celecoxib, which was followed by introduction of rofecoxib, valdecoxib, parecoxib, aceclofenac and etoricoxib.<sup>4</sup> At first glance, these COX-2 inhibitors look like the solution to NSAID complications like gastric ulcers,<sup>5</sup> transient rise in liver enzymes, occasionally even significant hepatitis, Reye's syndrome,<sup>6,7</sup> joint destruction (suppress bone repair and remodeling),<sup>8</sup> disturbed sleep pattern,<sup>9</sup> augment insulin secretion,<sup>10</sup> adverse psychiatric reactions like depressive disorders and suicidal tendencies,<sup>11</sup> CNS side effects (headache, aseptic meningitis, drowsiness, altered mood, tinnitus etc),<sup>7</sup> aplastic anemia and thrombocytopenia,<sup>7</sup> respiratory complications (pulmonary alveolitis and aggravation of asthmatic attack) and nephrotoxicity.<sup>7</sup> Although initial trials showed superiority of COX-2 selective drugs over nonselective drugs, but clinical experience has put their safety in question. The CLASS trial<sup>12</sup> demonstrated better safety of celecoxib than other drugs. In the VIGOR trial,<sup>13</sup> rofecoxib 50 mg per day was compared to naproxen 500 mg BID in 8076 patients with rheumatoid arthritis over a median treatment period of 9 months. Data from the above trial demonstrated fewer serious events in naproxen group than rofecoxib group. The cumulative risk of developing serious cardiovascular thrombotic events (more myocardial infarctions) was 1.7% in rofecoxib and 0.7% in naproxen

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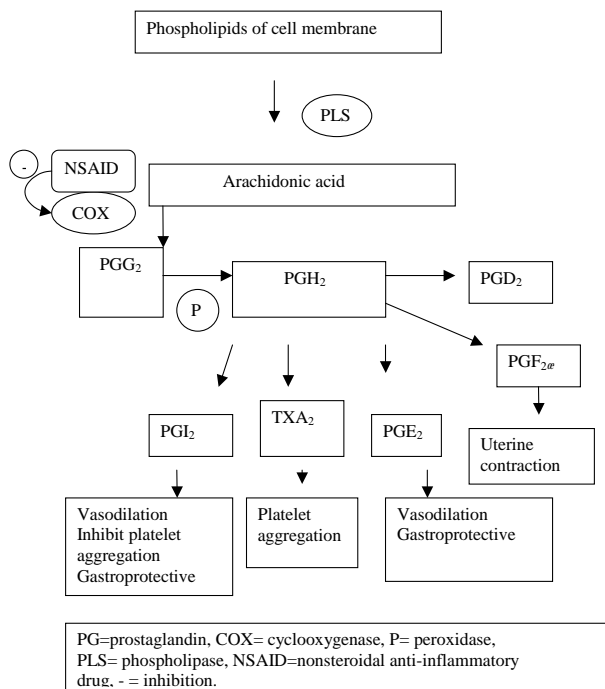


Fig. 1: Mechanism of action of NSAIDs

group.<sup>13</sup> Two large short-term randomized control trials (28 days) compared meloxicam with other NSAIDs in osteoarthritis patients. MELISSA<sup>14</sup> (9323 patients) compared meloxicam 7.5 mg daily with diclofenac SR 100 mg daily and SELECT<sup>15</sup> (8656 patients) compared meloxicam 7.5 mg daily with piroxicam 20 mg daily. Measures of efficacy in the meloxicam patients were significantly less than the comparator in both trials; however, complicated and symptomatic ulcers were uncommon and not significantly different.

## COX-2 INHIBITORS AND SAFETY CONCERNS

In January, 2004 the FDA launched an awareness campaign which was established to educate consumers about the potentially lethal side effects associated with the misuse of NSAIDs. The side-effect profile of NSAIDs varies with the specificity each drug has towards COX-1 or COX-2 (COX-1 to COX-2 specificity ratio).<sup>16</sup> COX-2 inhibitors may decrease vascular prostacyclin (PGI<sub>2</sub>) production and may affect the balance between prothrombotic and antithrombotic eicosanoids<sup>17</sup> and may tip the balance in favour of prothrombotic eicosanoids (thromboxane A<sub>2</sub>) and lead to increased cardiovascular thrombotic events.<sup>18</sup> In the Therapeutic Arthritis Research and Gastrointestinal Event Trial (TARGET), lumiracoxib, a highly selective COX-2 inhibitor that has been approved in the U.K. showed no significant differences in ulcer complications or cardiovascular endpoint (myocardial infarction, stroke, and cardiovascular death) when compared with ibuprofen.<sup>19</sup> However, it exhibited a trend toward more

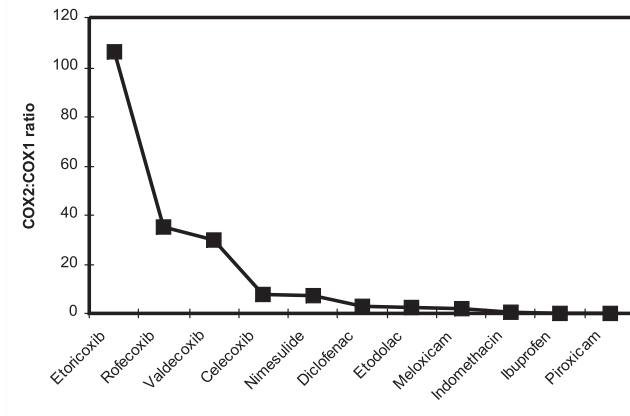


Fig. 2 : COX1:COX2 selectivity ratio of NSAIDs

myocardial infarction than naproxen, but these differences were not statistically significant.<sup>19</sup> COX-2 inhibitors have also been shown to increase blood pressure (BP). Rise in BP after NSAID use may be due to alterations in the renin angiotensin pathway, sodium and water retention by the kidney due to inhibition of vasodilating PG's and production of various vasoconstricting factors, including endothelin-1 and P450-mediated metabolites of arachidonic acid.<sup>20</sup> Locally synthesized PGI<sub>2</sub>, PGE<sub>2</sub> and PGD<sub>2</sub> cause vasodilatation, decreased vascular resistance and enhanced perfusion with redistribution of blood flow from the renal cortex to nephrons in the juxta-medullary region. Moreover, PGE<sub>2</sub> and PGF<sub>2μ</sub> cause diuresis by inhibiting the transport of Na and Cl in the thick ascending limb of loop of Henle and collecting ducts. Nephrotoxicity with NSAIDs includes acute tubular necrosis, acute tubulointerstitial nephritis, glomerulonephritis, renal papillary necrosis, salt and water retention, chronic renal failure, hypertension, hyperkalemia and hypoaldosteronism.<sup>21</sup> Macular eruptions, urticaria, pseudoporphyria and erythema multiforme have also been reported with COX-2 inhibitors.<sup>7</sup> However, early data suggested that COX-2 selective agents can be used safely in asthmatics.<sup>7</sup> Oedema, worsening of heart failure, fatal allergic vasculitis, and aggravation of doxorubicin-mediated and cardiac injury have also been reported with use of COX-2 selective inhibitors.<sup>22-25</sup>

## USE OF NSAIDS IN SPECIAL PHYSIOLOGICAL CONDITIONS

It has been reported that COX-2 inhibitors also interfere with implantation, hence their use should be avoided in sexually active women at risk of pregnancy.<sup>26</sup> Prostaglandins are involved in the development of numerous organ and physiologic systems such as the sleep cycle, cerebral blood flow, renal hemodynamics, thermoregulation, hemostasis, and the pulmonary, central nervous and cardiovascular systems.<sup>27</sup> There is evidence that the proper genesis of these systems may be adversely affected by NSAID exposure in utero and

during the neonatal period.<sup>27</sup> There have been numerous reports of nephrotoxicity in neonates that were exposed to NSAIDs at an early age.<sup>28</sup> Safety and efficacy of COX-2 inhibitors have not been evaluated in neonates. The COX-2 enzyme is also involved in the development of many organ systems, and its inhibition may lead to a prothrombotic state.<sup>27</sup> Heart disease is less pronounced in women than in men, but this difference narrows after menopause. It has been seen that prostacyclin can modulate gender differences in atherosclerosis and that estrogen increases prostacyclin.<sup>29</sup> In addition, it has been reported that estrogen upregulates COX-2-dependent prostacyclin, which contributes to the atheroprotective effect of estrogen.<sup>29</sup> Thus there is possibility of an interaction between hormone replacement therapy and drugs which inhibit COX-2, including traditional NSAIDs.

Moreover, COX-2 inhibitors are not deprived of drug interactions. They can increase plasma levels of warfarin by displacing it from protein binding site and can increase the risk of bleed.<sup>30</sup> They can decrease the clearance of methotrexate and lithium.<sup>30</sup> By decreasing synthesis of PGs in kidney they can increase nephrotoxicity induced by aminoglycosides, amphotericin B, cidofovir, cisplatin, cyclosporine, foscarnet, ganciclovir, pentamidine and vancomycin.<sup>30</sup> They can also decrease antihypertensive efficacy of beta-blockers, diuretics, angiotensin converting enzyme inhibitors, calcium channel blockers etc.<sup>30</sup>

### ADVANTAGES WITH SELECTIVE COX-2 INHIBITORS

American College of Rheumatology guidelines recommended that patients with at least one gastrointestinal risk factor receive either an NSAID plus a coprescribed protective agent or a COX-2 specific inhibitor, as does the national institute of clinical excellence in UK and the Dutch general practitioner guidelines.<sup>31-33</sup> NSAID's may influence inflammation by inhibiting COX-1 and COX-2 and by activating the peroxisome proliferators- $\gamma$  (PPAR- $\gamma$ ) nuclear transcription factor.<sup>34-36</sup> In addition, COX mediated oxidation is important in the calcium-dependent glutamate signaling pathway that involves N-methyl C-D aspartate. Thus, COX-2 inhibitors may be able to protect neurons directly by reducing cellular response to glutamate and have potential to reduce the risk of Alzheimer's disease in old patients, who are using NSAIDs for joint pains.<sup>37,38</sup> The prophylactic potential of COX-2 inhibitors against cancers is also well known.<sup>39</sup>

### CURRENT STATUS AND FUTURE DIRECTIONS

Since, their introduction, COX-2 specific inhibitors have become a rapidly growing segment of the prescription drug market, especially in patients of

osteoarthritis and rheumatoid arthritis. However, high cost of COX-2 specific inhibitors relative to nonselective NSAIDs has resulted in restriction on their use.<sup>40</sup> However, recently there is controversy regarding hepatic toxicity with nimesulide and cardiovascular complications with rofecoxib. FDA has banned the use of nimesulide in pediatric patients and rofecoxib in both adults and children. Both these drugs are freely available in Indian market. Following the worldwide withdrawal of rofecoxib, the European Medicines Agency (EMA) has been asked by the European Commission, as a precautionary measure, to conduct a review of COX-2 inhibitor medicines.<sup>41</sup> The CHMP, the Agency's scientific committee responsible for human medicines, will look at all aspects of cardiovascular safety of the COX-2 inhibitors like celecoxib, etoricoxib, lumiracoxib, parecoxib and valdecoxib, including thrombotic events (e.g. heart attack and stroke) and cardio-renal events (e.g. hypertension, oedema and cardiac failure).<sup>41</sup> The National Institutes of Health (NIH) has suspended the use of COX-2 inhibitor celecoxib for all participants in a large colorectal cancer prevention clinical trial (Adenoma Prevention with Celecoxib (APC) trial) conducted by the National Cancer Institute (NCI).<sup>42</sup> Furthermore, COX-2 inhibitors lose their selectivity after prolonged use.<sup>30</sup> Hence, pro-drugs are being developed with the aim of allowing absorption of inactive drug across the gastrointestinal mucosa without affecting prostaglandin synthesis until subsequent activation in the liver. Nabumetone is a COX-2 selective, non-acidic pro-drug having no enterohepatic recirculation with theoretically reduced GI adverse drug reactions.<sup>43</sup> Sulindac is another pro-drug with theoretical advantage of no adverse effects on the kidney as the active sulphide metabolite appears not to inhibit renal prostaglandin synthesis.<sup>44</sup> Other possible future alternatives to COX-2 selective inhibitors include nitric oxide (NO) NSAIDs. Like prostaglandins, nitric oxide protects the gastric mucosa. NO-NSAIDs have a nitric oxide moiety linked to a conventional NSAID, these drugs donate NO to the gastric mucosa to counterbalance the harmful effects of prostaglandin deficiency.<sup>45</sup> Studies in animals have shown a good gastrointestinal safety profile. However further work is needed to show their clinical value and to determine if they offer any practical advantages over COX-2 selective agents.

The choice of COX-2 selective inhibitors for a particular patient should be based upon a number of factors, including relative efficacy, toxicity, concomitant drugs, concurrent disease states, the patient's age, renal function, and cost. Differences in anti-inflammatory activity between NSAIDs in different groups is small but there is a wide variation in the incidence of side effects and in individual patient response. However, it is important to give each NSAID an appropriate therapeutic trial before an alternative is tried.

## REFERENCES

1. Infoscane Services, International analgesics category. Total food, drug and mass Merch, 52 weeks ending July 16, 2000. Plymouth and Pennsylvania: Information Resources Inc 2000.
2. Woodfork KA, Dyke KV. Anti-inflammatory and antirheumatic drugs. In: Craig CR, Stitzel RE, eds. *Modern Pharmacology with clinical applications*, 6th edition, Lippincott Williams and Wilkins-Philadelphia 2004:423-39.
3. Chandrasekharan NV, Dai H, Roos KL, Evanson NK, Tomsik J, Elton TS, Simmons DL. COX-3, a cyclooxygenase-1 variant inhibited by acetaminophen and other analgesic/antipyretic drugs: cloning, structure, and expression. *Proc Natl Acad Sci U S A* 2002;99:13926-31.
4. Hinz B, Brune K. Non-steroidal anti-inflammatory drugs-old and new. In: Isenberg DA, Maddison PJ, Woo P, Glass D, Breedveld FC. eds. *Oxford textbook of rheumatology*, 3rd edition, Oxford University Press Inc., New York 2004:442-50.
5. Graumlich JF. Preventing gastrointestinal complications of NSAIDs: risk factors, recent advances, and latest strategies. *Postgrad Med* 2001;109:117-28.
6. Morrow JD, Robert II LJ. Lipid-derived autacoids. Eicosanoids and platelet derived activating factor. In: Hardman GJ, Limbird E L, Gilman G A editors. *Goodman & Gilman's The Pharmacological basis of therapeutics* tenth edition Mc. Graw Hill Medical Publishing Division, New Delhi 2001:669-85.
7. Brooks PM. Non-steroidal anti-inflammatory drugs .In: Chochberg MC, Silman AJ, Smolen JS, Weinblatt ME, Weisman MH. eds. *Rheumatol*, 3rd edition (vol-I)-Mosby-London. 2004:377-84.
8. Dingle JT. The effects of NSAID on the matrix of human articular cartilages. *Z Rheumatol* 1999;58:125-9.
9. Murphy PJ, Badia P, Myers BL, Boecker MR, Wright KP. Nonsteroidal anti-inflammatory drugs affect normal sleep patterns in humans. *Physiol Behav* 1994;55:1063-6.
10. Metz SA, Robertson RP, Fujimoto WY. Inhibition of prostaglandin E synthesis augments glucose-induced insulin secretion in cultured pancreas. *Diabetes* 1981; 30:551-7.
11. Jiang HK, Chang DM. Non-steroidal anti-inflammatory drugs with adverse psychiatric reactions: five case reports. *Clin Rheumatol* 1999;18:339-45.
12. Silverstein FE, Faich G, Goldstein JL, et al. Gastrointestinal toxicity with celecoxib versus nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis. The CLASS study: a randomized controlled trial. *JAMA* 2000;284:1247-55.
13. Bombardier C, Laine L, Reicin A, et al. For the VIGOR Study Group. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. *N Engl J Med* 2000;343:1520-8.
14. Hawkey C, Kahan A, Steinbrück K, et al. Gastrointestinal tolerability of meloxicam compared to diclofenac in osteoarthritis patients. *Br J Rheumatol* 1998;37:937-945.
15. Dequeker J, Hawkey C, Kahan A, et al. Improvement in gastrointestinal tolerability of the selective cyclooxygenase (COX)-2 inhibitor, meloxicam, compared with piroxicam: results of the safety and efficacy large-scale evaluation of COX-inhibiting therapies (SELECT) trial in osteoarthritis. *Br J Rheumatol* 1998;37:946-951.
16. Mandal SP. Etoricoxib- A new, potent and highly selective COX-2 inhibitor. *JAMA-India* 2004;3:79-82.
17. Rang H P, Dale MM, Ritter JM. (eds). *Non-steroidal anti-inflammatory drugs*. In. *Pharmacology* 4th edition. Publisher Churchill Living Stone New York. 2000:229-35.
18. Belton D, Byrne D, Keamey D, Leahy A, Fitzgerald DJ. Cyclooxygenase 1 and 2 dependent Prostacyclin formation in patients with atherosclerosis. *Circulation* 2000;102: 840-5.
19. Cardiovascular Effects of COX-2 Inhibitors: The Jury's Still Out .Journal Watch (General) September 17, 2004, Posted 10/20/2004 ,Journal Watch 3(9), 2004. (c) 2004 Massachusetts Medical Society. Last assessed 22.12.04.
20. Frishman WH. Effects of non-steroidal anti-inflammation drug therapy on blood pressure and peripheral edema. *Am J Cardiol* 2002;89:18D-25D.
21. Ejaz P, Bhojani K, Joshi VR. NSAIDs and Kidney. *JAPI* 2004;52:632-9.
22. Pitkala KH, Strandberg TE, Tilvis RS. Worsening heart failure associated with COX-2 inhibitors. *Am J Med* 2002;112:424-6.
23. Schneider F, Meziari F, Chartier C, Alt M, Jaeger A. Fatal Allergic Vasculitis associated with celecoxib. *Lancet* 2002;359: 852-3.
24. Dowd NP, Scully M, Adderley SR, Cunningham AJ, Fitzgerald D J. Inhibition of cyclooxygenase-2 aggravates doxorubicin mediated Cardiac injury in vivo. *J Clin Invest* 2001;208:586-90.
25. Malhotra S, Shafiq N, Pandhi P. Cardiovascular adverse effects of COX-2 inhibitors. *Cardiology Today* 2002;V1:193-5.
26. Bermas BL. Drugs and pregnancy. In: Chochberg MC, Silman AJ, Smolen JS, Weinblatt ME, Weisman MH. eds. *Rheumatol*, 3rd edition (vol-I)-Mosby-London 2004.p.497-504.
27. Morris JL, Rosen DA, Rosen KR. Nonsteroidal anti-inflammatory agents in neonates. *Paediatr Drugs* 2003;5:385-405.
28. Cuzzolin L, Dal Cere M, Fanos V. NSAID-induced nephrotoxicity from the fetus to the child. *Drug Saf* 2001;24:9-18.
29. New findings have implications for chronic use of COX-2 Inhibitors in pre-menopausal women. News-Medical.Net, Posted By: News-Medical in Medical Research News, Published: Thursday, 18-Nov-2004 <http://www.med.upenn.edu/> last assessed 22.12.2004.
30. Robert II LJ, Morrow JD. Analgesic- antipyretic and anti-inflammatory agents and drugs employed in the treatment of gout. In: Hardman G J, Limbird E L, Gilman G A editors. *Goodman & Gilman's The Pharmacological basis of therapeutics* tenth edition Mc. Graw Hill Medical Publishing Division , New Delhi 2001:687-731.
31. Sturkenboom MCJM, Burke TA, Dieleman JP, Tangelder MJD, Lee F, Goldstein JL. Underutilization of preventive strategies in patients receiving NSAIDs. *Rheumatol* 2003;42(suppl.3):iii23-31.
32. Recommendations for the medical management of osteoarthritis of the hip and knee:2000 update. American college of Rheumatology. Subcommittee on osteoarthritis guidelines. *Arthritis Rheum* 2000;43: 1905-15.
33. National Institute of Clinical Excellence guidelines on the use of COX-II selective inhibitors celecoxib, rofecoxib, meloxicam and etodolac for osteoarthritis and rheumatoid arthritis. National Institute of Clinical Excellence. Technology appraisal guidance NO 27. Available at <http://www.nice.org.uk/pdf/coxiifullguidance>.
34. Lehmann JM, Lenhard JM, Oliver BB, Ringold GM, Kliewer S A. Peroxisome proliferators-activated receptors alpha and gamma are activated by indomethacin and other non-steroidal anti-inflammatory drugs. *J Biol Chem* 1997;272:3406-10.
35. Ricole M, Li A C, Willson T M, Kelly C J, Glass C K. The Peroxisome proliferator-activated receptor - gamma is a negative regulator of macrophage activations. *Nature* 1998;391:79-82.
36. Leveugle B, Fillit H. Proteoglycans and the acute- phase response in Alzheimer's disease brain. *Mol Neurobiol* 1994;9:25-32.
37. Breitner JC. Inflammatory processes and anti-inflammatory drugs in Alzheimer's disease : a current appraisal. *Neurobiol Aging* 1996;17:789-94.

38. Vfid BA, Ruitfnrfrg A, Hofman A, *et al.* Nonsteroidal anti inflammatory drugs and the risk of Alzheimer's disease. *N Eng J Med* 2001;345:1615-21.
39. Demierre MF, Nathanson L. Chemoprevention for melanoma: An unexplored Strategy. *J Clin Oncol* 2003;21:158-65.
40. Lelorier J, Fitzsimon C, Keresteci M, StewartR, Lavoie F. Drug utilization review of celecoxib in Ontario. *Rheumatol* 2003;42(S3):iii11-6.
41. News-Medical.Net Following the withdrawal of Vioxx, the European Medicines Agency has been asked to review of COX-2 inhibitor medicines .Posted By: News-Medical in Pharmaceutical News, Published: Monday, 25-Oct-2004,last Assessed23.12.04.
42. Celebrex suspension, Posted By: News-Medical in Pharmaceutical News. J News-Medical. Net, journal Watch 3(9), 2004. (c) 2004 Massachusetts Medical Society, Published: Sunday, 19-Dec-2004, last assessed23.12.04.
43. Choy EHS, Scott DL. Drug treatment of rheumatic disease in the 1990s: Achievements and future developments. *Drugs* 1997;53:337-48.
44. Inflammation, arthritis and non-steroidal anti-inflammatory drugs (NSAIDs). In: Laurence DR, Bennett PN, Brown MJ, editors. *Clinical Pharmacology*. 8th ed. Edinburgh: Churchill Livingstone, 1992:249-59.
45. Wood J. Musculoskeletal disorders. Rheumatoid arthritis: the disease and its management with NSAIDs. *The Pharmaceutical J* 1999;262:881-4.

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