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Risks of nonsteroidal antiinflammatory drugs (NSAIDs)

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Abstract

Nonsteroidal antiinflammatory drugs (NSAIDs) are among the most frequently used medicines all over the world. Several studies emphasized that all NSAIDs may potentially be harmful not only on the gastrointestinal (GI), but also on the cardiovascular (CV) system, as they can increase the blood pressure, the risk of coronary events (angina, myocardial infarction), and that of stroke, as well as they may deteriorate renal functions. There are substantial unequalities between different compounds, and the NSAID-induced CV risk does not depend on the ratio of COX-1/COX-2 selectivity. The newly available data of original papers and metaanalyses shed light on further details. Even naproxen which drug was previously considered the less harmful can increase the risk of blood pressure, stroke, an gastrointestinal (GI) complications. It has to be emphasized that the most important risk of NSAIDs is still the GI hemorrhage. This adverse effect is significantly less for drugs which are more selective for COX-2 than COX-1 enzyme, but other, pleiotropic effects can also beneficially modify the GI as well as the CV risk. E.g. the aceclofenac was found to be among NSAIDs with the less adverse effects on GI system and is also among those having the less CV risk.

Keywords: resistant hypertension, baroreceptors, carotid baroreceptor stimulation

Introduction

Nonsteroidal antiinflammatory drugs (NSAID) are among the most frequently and on long-term used medicines in the world. Some of them (e.g. diclofenac) are available over the counter (OTC). Cardiovascular (CV) risk is increasing with age and so does the prevalence of the so called rheumatic diseases (rheumatoid arthritis, osteoarthritis etc.), therefore the use of NSAIDs are more frequently used in the elderly patients, sometime without informing their physicians. Mechanisms of action of NSAIDS involve inhibition of both, cyclooxygenase-1 and cíclooxygenase-2 (COX-1, COX-2) enzymes. As a consequence, they have antiinflammatory and pain-releiving acion. Several drugs with different chemical sructure have been synthesized and got into the clinical practice (aceclofenac, celecoxib, dixlofenac, etoricoxib, ibuprofen, indometacin, ketoprofen, naproxen, nifluminsav, piroxicam). These are thought to be more selective for the COX-2 enzyme are called as „coxibs", howewer, some of them - such as diclofenac - is more selective for the COX-2 than celecoxib [1]. Therefore the denomination as „coxib" should be questioned.

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Risks of NSAIDs was recently summarised [2]. In the following paper I will shortly describe the most important cardiovascular, renal and gastrointestinal side effects of NSIDs.

NSAIDs and CV risk

Those drugs that mostly inhibit COX-2 enzyme do not decrease platelet aggregation, consequently the risk of GI bleeding is relatively small, but they do not decrease CV risk, rather increase it because of inhibition of synthesis of vasodilatory prostaglandins (PGE-2 and PGI-2) and relative increase in thromboxán A2 (TXA-2). In addition to this, inhibition of COX-2 enzyme increase CV risk by other mechanisms such as increase of blood presure (BP), decrease of angiogenesis and destabilisation of atherosclerotic plaques [3–13]. An interesting new result have been published showing that ibuprofen or naproxen inhibits the antiplatelet effect of aspirin while meloxicam or etoricoxib have no such an efect [13]. In the Mini-COREA study celecoxib (daily dose of 400mg for 3 months) inhibited the decrese in the lumen of the stent implanted after myocardial infarction (p=0.02) by 0.09 mm, but the primary end point of the study (reinfarcion + CV death) was increased by 1.6 % [14].

Another study showed that naproxen increased office BP and ambulatory blood pressure monitoring values in patients treated by ramipril or valsartan, but not of those patients who have been treated by the direct renin inhibitor, aliskiren. On the other hand. acetaminofen inhibited antihypertensive effects of all, ramipril, valsartan or aliskiren treatment [15].

The unwanted vascular effects of classical NSAIDs and COX-2 inhibitors was summarised in a metaanalysis of 280 randomised, placebo-contrtolled studies including data of 124. 513 patients (68342 patient-years), and 424 studies comparing two NSAIDs including data of 229.296 patients (165. 456 patient-years) leading to the conclusion that coxibs and diclofenac increased the number of major vacular events by 30% mainly by the increase in major coronary events and coronary death. Ibuprofen also significantly increased incidents of coronary events but not of major vascular events. Naproxen did not increase incidents of major vascular events nor that of vacular death. All NSAIDs and coxibs increased the risk of developing hear failure [16].

In the prospecive population-based Rotterdam study analysis of data (standardised to age, gender, CV risk factors – blood presure, body mass index, blood lipids, smoking) of 8423 patients showed that NSAID therapy even for a short time (2–4 weeks) increased the risk of developing atrial fibrillation by 76% as compared to data of those who have not been treated by NSAIDs [17].

NSAIDs and renal risk

It is well known for a long time that NSAIDs may cause renal damage on long-term administration. In the UK Clinical Practice Research Datalink data of 487.372 patients treated by antihypertensive drugs were summarised between the years of 1997–2008 to reveal the possible renal adverse effects (hospitalisation for acute kidney failure) of NSAIDs added

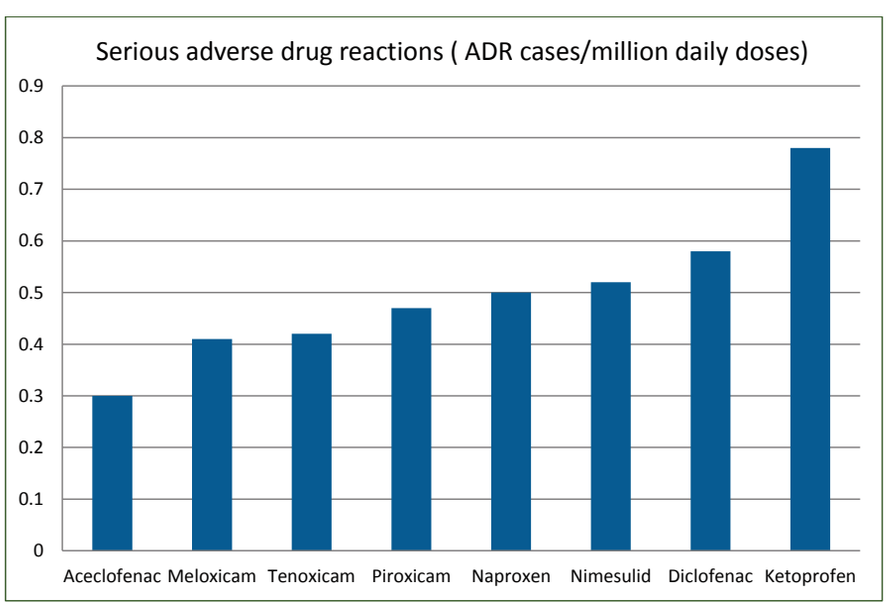

Figure 1. Serious adverse drug reactions (ADR cases/million daily doses).

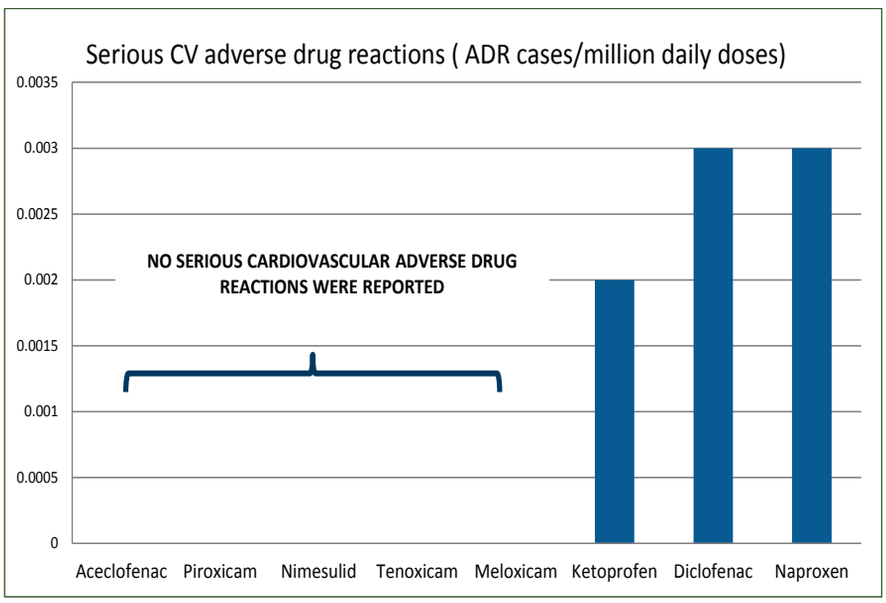

Figure 2. Serious CV adverse drug reactions (ADR cases/million daily doses).

to diuretic (DIU), or to angiotensin convering enzyme inhibitors (ACEI), or to angiotensin II AT-1 receptor antagonists (ARB) or to the combination of ACEI+DIU or to that of ARB+DIU. NSAIDs added to ACEI, or to ARB did not have unwanted adverse effects, but added to the combination of ACEi+DIU or to ARB+DIU it increased risk of acute renal failure [18]. Editorial of British Medical Journal emphasized that standard deviation of data is large therefore it is possible that the average values of data may underestimate the renal risk [19, 20].

NSAIDs and gastrointestinal risk

It is well accepted that the most frequent risk of treatment with NSAIDs is the increase of gatrointestinal (GI) events (ulcers, bleeding). A study comparing the risks of GI events patients treated by different NSAIDs showed, that the highest GI risk was with ketorolac (OR: 24.7), then with indomethacin, ketoprofen , naproxen (OR : 10.0), aspirin (OR: 8.0), rofecoxib (7.3), meloxicam (OR: 5.7), dexketoprofen (OR: 4.9), diclofenac (OR: 3.3), nimesulid (OR: 3.2), ibupro-

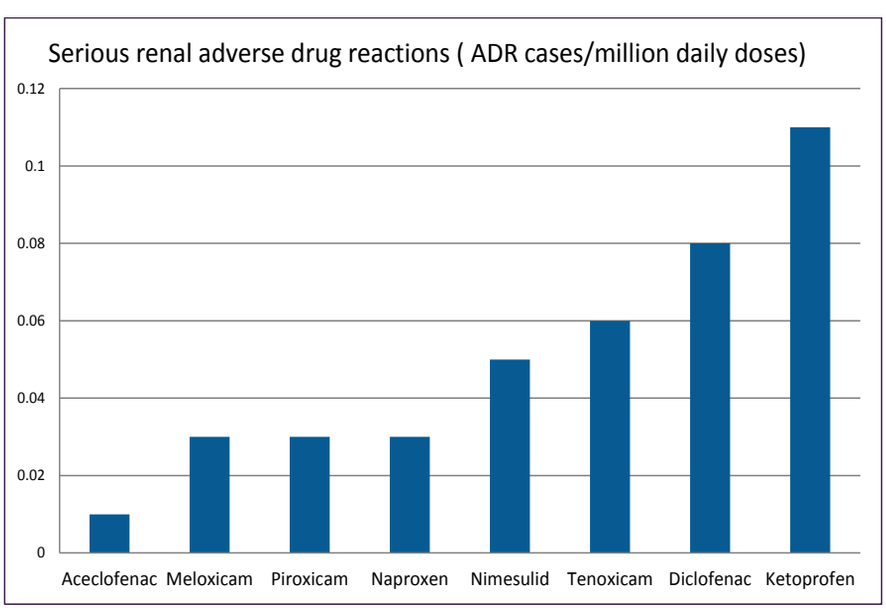

Figure 3. Serious renal adverse drug reactions (ADR cases/million daily doses).

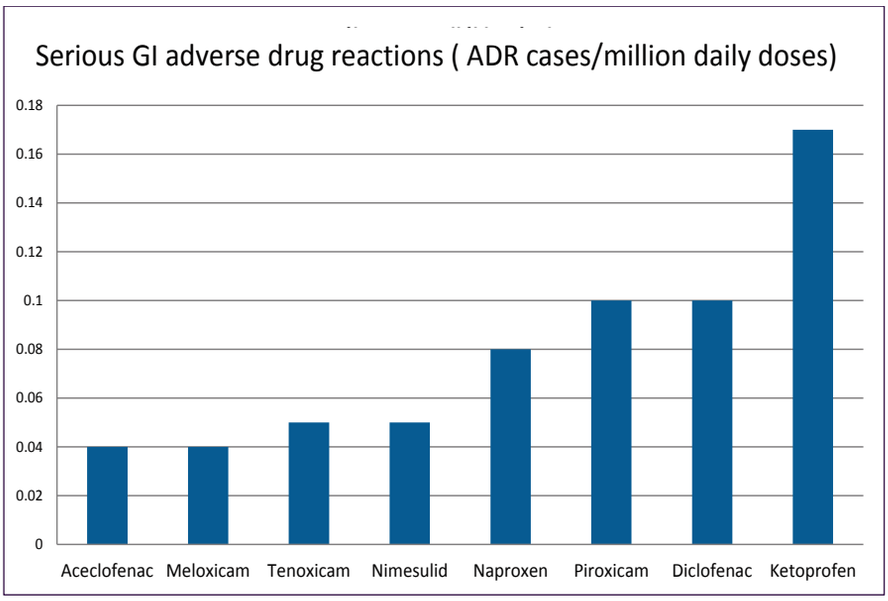

Figure 4. Serious GI adverse drug reactions (ADR cases/million daily doses).

fen (OR: 3.1), while the smaller risk was with acelofenac (1.4) and celecoxib (OR: 0.3) [21]. Somewhat similar results were published in a study where major CV events, heart failure and GI adverse effects (upper GI event and GI bleeding) were compared in patients treated by coxibs, or diclofenac, or ibuprofen or naproxen. Risk of major CV events with coxibs and diclofenac were higher then with ibuprofen or naproxen, while the risk of heart failure was not different. All NSAIDs increased the risk of GI events, the risk of upper GI events was the lowest with coxibs (OR: 1.81), and diclofenac (OR: 1.89), and higher with ibuprofen (OR: 3.97), and the highest was with naproxen (OR: 4.22) [22]. A study in Japan including data of patients with diverticulosis colontos the hemorrhagic risk increased with loxoprofen (OR: 5.0), diclofenac (OR: 3.1), etodolac (OR: 4.9), aspirin (OR: 3.9). The increase od risk was 23-fold when aspirin + NSAID was used [23].

Although pharmacovigilance studies are not considered as those with high level evidence, it is interesing to show the results of a study colleting data of reports of side effects of different NSAIDs betwen the years 2002 to 2006 in France [24].

Conclusions

1. Serious adverse drug reactions were reported less frequently with aceclofenac, most frequently with diclofenac and ketoprofen (Figure 1);
2. Cardiovascular adverse dug reactions are not related to the ratio of COX-1 / COX-2 inhibition (Figure 2).
3. Renal adverse drug reactions were reported less frequently with aceclofenac, most frequently with dilofenac andketoprofen (Figure 3);
4. GI adverse drug reactions were less frequently reported with COX-2-selective NSAIDs and with aceclofenac (a non COX-2 selective drug). Aceclofenac has many pleiotropic effects not related to the inhibition of COX enzymes. These effects may be gastroprotective (Figure 4).

References

1. Warren TD., Michel JA. COX-selectivity of Nosteroidal Inatiinflammatory Drugs. FASEB 204; 18:790-804.
2. Sudano I, Flammer AJ, Roas S, Enseleit F, Noll G, Ruschitzka F Nonsteroidal Antiinflammatory Drugs, Acetaminophen, and Hypertension. Curr Hypertens Rep (2012) 14:304–309
3. Pope JE, Anderson JJ, Felson DT. A meta-analysis of the effects of nonsteroidal anti-inflammatory drugs on blood pressure. Arch Intern Med. 1993;153(4):477–84.
4. Wilson SL and Poulter NR The effect of non-steroidal antiinflammatory drugs and other commonly used non-narcotic analgesics on blood pressure level in adults. J. Hypertens. 2006; 24:1457–1469
5. Whelton A, White WB, Bello AE, et al. Effects of celecoxib and rofecoxib on blood pressure and edema in patients _65 years of age with systemic hypertension and osteoarthritis. Am J Cardiol. 2002;90:959 –963
6. Farkouh ME, Verheugt FW, Ruland S, et al. A comparison of the blood pressure changes of lumiracoxib with those of ibuprofen and naproxen. J Clin Hypertens. 2008;10:592–602

7. Howard PA, Delafontaine P. Nonsteroidal anti-inflammatory drugs and cardiovascular risk. J Am Coll Cardiol 2004;43:519-525
8. Konstam MA, Weir MR, Reicin A, et al. Cardiovascular thrombotic events in controlled, clinical trials of rofecoxib. Circulation 2001;104:2280-2288
9. Weir MR, Sperling RS, Reicin A, Gertz BJ. Selective COX-2 inhibition and cardiovascular effects: a review of the rofecoxib development program. Am Heart J 2003;146:591-604
10. Solomon DH, Glynn RJ, Levin R, Avorn J. Nonsteroidal anti-inflammatory drug use and acute myocardial infarction. Arch Intern Med 2002;162:1099-1104
11. Solomon DH, Schneeweiss S, Glynn RJ, et al. Relationship between selective cyclooxygenase-2 inhibitors and acute myocardial infarction in older adults. Circulation 2004;109: 2068-2073
12. Strand V, Hochberg MC. The risk of cardiovascular thrombotic events with selective cyclooxygenase-2 inhibitors. Arthritis Rheum 2002;47:349-355
13. Meek IL, Vonkeman HE, Kasemier J, Movig KL, et al. Interference of NSAIDs with the thrombocyte inhibitory effect of aspirin: A placebo-controlled, ex vivo, serial placebo-controlled serial crossover study. Eur J Clin Pharmacol. 2012 Aug 14.
14. Kang H-J, Oh I-Y, Chung J-W, et al. Effects of Celecoxib On Restenosis after Coronary Intervention and Evolution of Atherosclerosis (Mini-COREA) trial: celecoxib, a double-edged sword for patients with angina. Eur Heart J 2012;33:2653–2661.
15. Gualtierotti R, Zoppi A, Mugellini A, et al. Effect of naproxen and acetminophen on blood presure lowering by ramipril, valsartan and aliskiren in hypertensive patients. Expert Opinion On Pharmacotherapy 2013;14:1875-84. doi: 10.1517/14656566.2013.816286.
16. Coxib and traditional NSAID Trialists' (CNT) Collaboration. Vascular and upper gastrointestinal effects of non-steroidal anti-inflammatory drugs: meta-analyses of individual participant data from randomised trials. Lancet. 2013 May 29. pii: S0140-6736(13)60900-9. doi: 10.1016/S0140-6736(13)60900-9.
17. Krijthe BP, Heeringa J, Hofman A. et al. Non-steroidal anti-inflammatory drugs and the risk of atrial fibrillation: a population-based follow-up study. BMJ Open 2014;4:e004059 doi:10.1136/bmjopen-2013-004059
18. Kohli P, Steg G, Cannon CP et al. on behalf of the REACH Registry Investigators. NSAID Use and Association with Cardiovascular Outcomes in Outpatients with Stable Atherothrombotic Disease. Am. J. Med. 2014; 127: 53-60
19. Lapi F, Azoulay L, Yin H, et al. Concurrent use of diuretics, angiotensin converting enzyme inhibitors, and angiotensin receptor blockers with non-steroidal anti-inflammatory drugs and risk of acute kidney injury: nested case-control study. BMJ 2013;DOI:10.1136/bmj.e8525. Available at: http://www.bmj.com.
20. Nitsch D and Tomlinson LA. Safety of coprescribing NSAIDs with multiple antihypertensive agents. BMJ Editorial 2013; DOI:10.1136/bmj.e8713. Available at: http://www.bmj.com.
21. Laporte JR, Ibáñez L, Vidal X, et al. Upper gastro-intestinal bleeding associated with the use of NSAIDs New vs. older agents. Drug Safety 2004;27:411-20
22. Colin Baigent et al. Vascular and upper gastrointestinal effects of non-steriodal anty-inflammatory drugs: meta-analyses of individual participant data from randomised trials. Lancet 2013; 382: 769-79.
23. Nagata N1, Niikura R, Aoki T. et l. Colonic diverticular hemorrhage associated with the use of NSAIDs, low-dose aspirin, antiplatelet drugs, and dual therapy. J Gastroenterol Hepatol. 2014 Apr 10. doi: 10.1111/jgh.12595.
24. Lapeyre-Mestre M, Grolleau S , Montastruc JL. Adverse drug reactions associated with the use of NSAIDs: a case/noncase analysis of spontaneous reports from the French pharmacovigilance database 2002-2006. Fundam Clin Pharmacol. 2013 Apr;27(2):223-30. doi: 10.1111/j.1472-8206.2011.00991.x. Epub 2011 Sep 20.