Reassessment of the benefit/risk-ratio of selective COX-2-inhibitors

Ulrich Klotz

Dr. Margarete Fischer-Bosch-Institute of Clinical Pharmacology, Stuttgart, Germany

Nonsteroidal anti-inflammatory drugs (NSAIDs) are among the most widely prescribed drugs worldwide, and gastrointestinal toxic effects induced by NSAIDs are quite common. However it must be emphasized that there is a considerable variability in the risk of gastrointestinal complications of the individual drug with ibuprofen and diclofenac showing the lowest toxic potential. In addition, infection by Helicobacter pylori (Hp) will independently increase the risk for inducing a peptic ulcer or ulcer bleeding [1, 2].

It is well known that both – therapeutic and toxic effects of NSAIDs – are mediated by the inhibition of cyclooxygenases (COX). Since the early 1990's it has been defined that two enzymes, COX-1 and COX-2, are responsible for the biosynthesis of various prostanoids (eg PGE_2, PGI_2, TxA_2) [3]. According to the working hypothesis that "constitutive" COX-1 is responsible for the physiological production of prostanoids ("housekeeping" enzyme) and "inducible" COX-2 for the elevated production of prostanoids at sites of inflammation, selective COX-2-inhibitors have been developed in the hope of more specific anti-inflammatory action and less (gastrointestinal) side effects. However, it is now obvious that also COX-2 is expressed constitutively in several tissues such as brain, kidney, pancreas, intestine, and blood vessels, which has implications for the toxic potential (eg renal, cardiovascular) of selective COX-2-inhibitiors [3].

Due to an aggressive marketing the expensive COX-2-inhibitors (eg celecoxib, rofecoxib) rapidly gained wide popularity among the prescribing physicians who believed in the propagated reduced profile of adverse effects especially concerning the gastrointestinal (GI) tract. Two independent studies, the CLASS-study (celecoxib vs ibuprofen or diclofenac) and the VIGOR-study (rofecoxib vs naproxen), concluded that intake of both COX-2-inhibitors was associated with a decrease in upper GI toxicity when compared to other NSAIDs [4, 5]. The provided results were generated in highly selected patients that did not represent general patient populations. Both studies were extensively criticized by numerous independent experts regarding study design, data analysis and publishing policy. From the beginning it was obvious that at least rofecoxib was associated with an increased risk for cardiovascular events [5], and that the gastrointestinal benefit of COX-2-inhibitors was at best marginal [6, 7] and completely lost if the patients had to take acetylsalicylic acid (aspirin) [4].

The recent (Sept. 30, 2004) world-wide withdrawal of rofecoxib, a selective COX-2-inhibitor approved by the FDA in 1999, triggered a hot debate regarding safety issues, in particular cardiovascular toxicity of rofecoxib and other COX-2-inhibitors such as celecoxib, valdecoxib or lumiracoxib.

In numerous articles the benefit/risk ratios of COX-2-inhibitors were controversially discussed. Based on prior publications, comprehensive data analysis and a recent cumulative meta-analysis it is now evident that long-term use of rofecoxib is associated with an elevated cardiovascular risk. Its withdrawal from the market was justified and should have been initiated already earlier [8]. A cautionary flag about the risk of cardiovascular events with COX-2-inhibitors especially rofecoxib was raised already in 2001 by reanalysing several trials [9]. Concerns were shared by the FDA who implemented labelling changes after a long discussion in 2002 which had, as expected, no impact on the prescription pattern of the drugs. Finally, data from a placebo-controlled trial with rofecoxib (25 mg per day) for the prevention of adenomatous polyps (APPROVe study) unequivocally proved in September 2004 the significant increase (as in the VIGOR study) in the incidence of serious thromboembolic adverse events for the rofecoxib group.

Whether other coxibs have the same toxic potential is very likely, as in December 2004 the "Adenoma Prevention" study with celexocib was stopped for the same reasons as the APPROVe study: patients on celecoxib (2 × 200 or 400 mg/day) had dose-dependently a 2.5 and 3.4 fold increased risk for cardiovascular events when compared to placebo (http://www.fda.gov/bbs/topics/news/2004/new01144.html). Moreover, two randomized, placebo-controlled trials in patients after coronary-artery bypass grafting showed that valdecoxib increased the risk of serious cardiovascular outcomes by a factor of approximately 3 [10]. The very similar cardiovascular toxicity of the coxibs can be explained by their common mechanism of action. Both, rofexoxib and celecoxib suppress the formation of prostacyclin (PGI_2), predomi-

nantly produced by COX-2 in endothelium and inhibiting platelet aggregation, causing vasodilatation and preventing proliferation of vascular smooth-muscle cells. These effects contrast with those of thromboxane (TxA_2), the major COX-1 product of platelets, which causes platelet aggregation, vasoconstriction and vascular proliferation. Thus, selective COX-2-inhibitors provoke a metabolic shift towards TxA_2 and consequently predispose patients to myocardial infarction or thrombotic stroke [11].

Concerning the well-documented cardiovascular risks of rofecoxib, the deliberate ignorance of the drug company and the slow reactions of drug agencies [12, 13] have damaged our confidence in ethical and unbiased decision processes. Moreover, the beneficial value of COX-2-inhibitors in terms of better GI-tolerability has been greatly exaggerated and is flawed for several methodological reasons [14]. It has been calculated that in clinical practice the estimated number need to treat (NNT) patients for 1 year to avoid one hospitalization for peptic ulcer disease is 157, whereas the estimated NNT to cause one myocardial infarction is 70 patients [15]. Thus, the benefit/risk-ratio of rofecoxib and that of other coxibs does not justify their broad use.

As the claimed therapeutic progress and favourable safety of COX-2-inhibitors remain so far elusive, it should be recalled that classical NSAIDs are clinically at least as effective as the coxibs, and some of them (eg ibuprofen, diclofenac) have only a slightly elevated risk for gastrointestinal adverse drug reactions (ADR). According to a recent analysis from the French pharmacovigilance database on reports of serious oeso-gastro-duodenal ADR coxibs had even a higher adjusted odds ratio (14.9) than diclofenac (9.2) or ibuprofen (7.3) indicating that the "real world" situation (where many patients take also aspirin!) will be different from clinical studies with preselected patients [16].

To prevent NSAID- and coxib-induced gastropathy coprescription of "gastroprotective" agents should be used in patients of known risk. From the different approaches currently available, proton pump inhibitors (PPI) represent drugs of first choice [17], and among them omeprazole has been most extensively studied.

Finally, one has to address the question: do we really need the expensive COX-2-inhibitors as (according to their benefit/risk ratio) a therapeutic progress can hardly be seen or do we still rely on NSAIDs like ibuprofen or diclofenac with their good long-term records regarding efficacy and safety? If there is a clear indication for a NSAID the following simplified strategy could be followed:

no	←	Patient with risk factors for GI-events (including Hp that should be eradicated with ulcus anamnesis)	→	yes
↓				↓
NSAID				NSAID + PPI

It should be realized that also the combined regimen can not completely prevent NSAID-induced GI-lesions, however the present COX-2-inhibitors can not be regarded as a real alternative. In the (near) future novel therapeutic principles like NO-NSAIDs or dual COX/LOX-inhibitors (eg licofelone) might offer some therapeutic progress.

In the second half of February 2005 the Committee for Medicinal Products for Human Use (CHMP) of the European Drug Agency (EMEA) has required a very restrictive use of all coxibs. Patients with cardiovascular risk factors (eg hypertension, hyperlipidemia, diabetes, smoking, coronary heart disease, history of stroke, occlusive arterial disease, congestive heart failure (NYHA II–IV) should not use the coxibs. Unexpectedly, at the same time the FDA came to the decision that there are not sufficient data for a withdrawal of rofecoxib. Apparently the FDA has problems to find the correct balance between risks and benefits of a drug [18]. Nevertheless based on unequivocal evidence that coxibs (eg rofecoxib, celecoxib) elevate the risk for cardiovascular events approximately by factor 2 to 4 only a very restrictive short-term use of coxibs appears to be feasible. However, it still remains questionable whether this class of NSAID is actually needed.

Note added in proof

Very recently three placebo-controlled studies with rofecoxib, celecoxib and parecoxib/valdecoxib have shown a 2- to 3.7-fold increased risk for severe cardiovascular adverse events [19–21] indicating that the cardiovascular toxicity represents a group effect of the coxibs [22, 23].

Acknowledgement: The work was supported by the Robert Bosch Foundation Stuttgart. The secretarial help of Mrs. Hengemühle is highly appreciated.

Correspondence:
Prof. Dr. Ulrich Klotz
Dr. Margarete Fischer-Bosch-Institut
für Klinische Pharmakologie
Auerbachstraße 112
D-70376 Stuttgart
E-Mail: ulrich.klotz@ikp-stuttgart.de

References

1 Henry D, Lim LL-Y, Rodriguez LAG, Carsdon JL, Griffin M, Logan R, et al. Variability in risk of gastrointestinal complications with individual non-steroidal anti-inflammatory drugs: results of a collaborative meta-analysis. Br Med J 1996;312: 1563–6.

2 Huang J-Q, Sridhar S, Hunt RH. Role of Helicobacter pylori infection and non-steroidal anti-inflammatory drugs in peptic-ulcer disease: a meta-analysis. Lancet 2002;359:14–22.

3 Warner TD, Mitchell JA. Cyclooxygenases: new forms, new inhibitors, and lessons from the clinic. FASEB J 2004;18:790–804.

4 Silverstein FE, Faich G, Goldstein JL, Simon LS, Pincus T, Whelton A, et al. Gastrointestinal toxicity with celecoxib vs nonsteroidal anti-inflammatory drugs for osteoarthritis and rheumatoid arthritis: the CLASS study: a randomized controlled trial. Celecoxib Long-term Arthritis Safety Study. JAMA 2000;284:1247–55.

5 Bombardier C, Laine L, Reicin A, Shapiro D, Burgos-Vargas R, Davis B, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. VIGOR study group. N Engl J Med 2000;343:1520–8.

6 Jüni P, Rutjes AWS, Dieppe PA. Are selective COX2 inhibitors superior to traditional non steroidal anti-inflammatory drugs? Br Med J 2002;324:1287–8.

7 Topol E, Falk GW. A coxib a day won't keep the doctor away. Lancet 2004;364:639–40.

8 Jüni P, Nartey L, Reichenbach S, Sterchi R, Dieppe PA, Egger M. Risk of cardiovascular events and rofecoxib: cumulative meta-analysis. Lancet 2004;364:2021–9.

9 Mukherjie D, Nissen SE, Topol EJ. Risk of cardiovascular events associated with selective COX-2 inhibitors. JAMA 2001; 286:954–9.

10 Ray WA, Griffin MR, Stein CM. Cardiovascular toxicity of valdecoxib. N Engl J Med 2004;351:2767.

11 FitzGerald GA. Coxibs and cardiovascular disease. N Engl J Med 2004, 351:1709–11.

12 Topol EJ. Rofecoxib, Merck, and the FDA. N Engl J Med 2004;351:2877–8.

13 Oberholzer-Gee F, Inamdar SN. Merck's recall of rofecoxib – a strategic perspective. N Engl J Med 2004;351:2147–49.

14 Cerezo JG, Hristov RL, Sansuán AJC, Rodriguez JJV. Outcome trials of COX-2 selective inhibitors: global safety evaluation does not promise benefits. Eur J Clin Pharmacol 2003;59: 169–75.

15 Jüni P, Reichenbach S, Dieppe PA, Egger M. Discontinuation of Vioxx. Lancet 2005;365:26–7.

16 Lugardon S, Lapeyre-Mestre M, Montastruc JL, The French Network of Regional Pharmacovigilance Centres. Upper gastrointestinal adverse drug reactions and cyclo-oxygenase-2 inhibitors (celecoxib and rofecoxib): a case/non-case study from the French Pharmacovigilance Database. Eur J Clin Pharmacol 2004;60:673–7.

17 Becker JC, Domschke W, Pohle T. Current approaches to prevent NSAID-induced gastropathy – COX selectivity and beyond. Br J Clin Pharmacol 2004;58:587–600.

18 Frantz S. How to avoid another "Vioxx". Nature Rev Drug Discovery 2005;4:5–7.

19 Bresalier RS, Sandler RS, Quan, H, Bolognese JA, Oxenius B, Horgan K, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. N Engl J Med 2005;352:1092–102.

20 Solomon SD, McMurray JJV, Pfeffer MA, Wittes J, Fowler R, Finn P, et al. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. N Engl J Med 2005;352:1071–80.

21 Nussmeier NA, Whelton AA, Brown MT, Langford RM, Hoeft A, Parlow JL, et al. Complications of the COX-2 inhibitors parecoxib and valdecoxib after cardiac surgery. N Engl J Med 2005;352:1081–91.

22 Drazen JM. COX-2 inhibitors – a lesson in unexpected problems. N Engl J Med 2005;352:1131–2.

23 Psaty BM, Furberg CD. COX-2 inhibitors-lessons in drug safety. N Engl J Med 2005;352:1133–5.

Swiss
Medical Weekly

Official journal of
the Swiss Society of Infectious disease
the Swiss Society of Internal Medicine
the Swiss Respiratory Society

The many reasons why you should choose SMW to publish your research

What Swiss Medical Weekly has to offer:

- SMW's impact factor has been steadily rising, to the current 1.537
- Open access to the publication via the Internet, therefore wide audience and impact
- Rapid listing in Medline
- LinkOut-button from PubMed with link to the full text website http://www.smw.ch (direct link from each SMW record in PubMed)

- No-nonsense submission – you submit a single copy of your manuscript by e-mail attachment
- Peer review based on a broad spectrum of international academic referees
- Assistance of our professional statistician for every article with statistical analyses

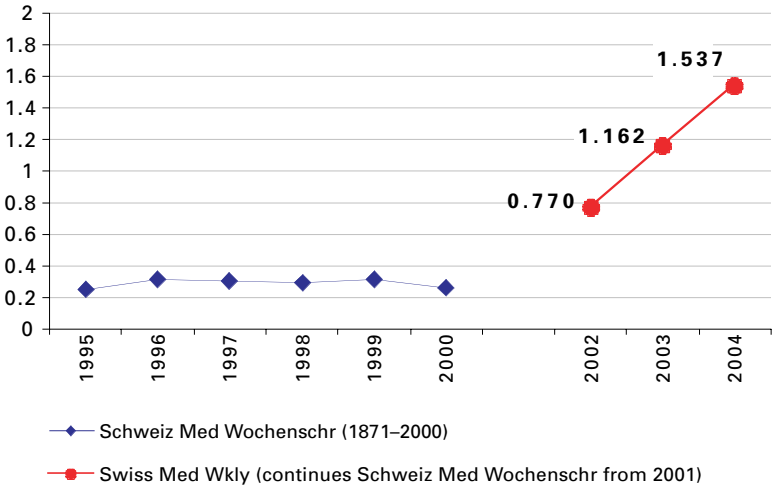
- Fast peer review, by e-mail exchange with the referees
- Prompt decisions based on weekly conferences of the Editorial Board
- Prompt notification on the status of your manuscript by e-mail
- Professional English copy editing
- No page charges and attractive colour offprints at no extra cost

We evaluate manuscripts of broad clinical interest from all specialities, including experimental medicine and clinical investigation.

We look forward to receiving your paper!

Guidelines for authors:
http://www.smw.ch/set_authors.html

Impact factor Swiss Medical Weekly



EMH FMH Schwabe
Editores Medicorum Helveticorum

All manuscripts should be sent in electronic form, to:

EMH Swiss Medical Publishers Ltd.
SMW Editorial Secretariat
Farnsburgerstrasse 8
CH-4132 Muttenz

Manuscripts: submission@smw.ch
Letters to the editor: letters@smw.ch
Editorial Board: red@smw.ch
Internet: http://www.smw.ch