COX-2 selective inhibitors – they are still the best treatment for many patients!

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The discussion of the selective cyclooxygenase-2 inhibitors during the last months was often more characterised by emotions than rationale. After years of euphoric acclaims by patients and physicians regarding the therapeutic success of rofecoxib, the negative results of the APPROVE-study (table 1) changed the public opinion and led to a condemnation of all cyclooxygenase-2 inhibitors. In the APPROVe-study rofecoxib (Vioxx®) was associated with a reduced occurrence of polyps, but also with an increase in cardial infarctions after chronic use of 25 mg/day for 1.5 years. This latter unexpected finding from an off-label long-term use, led to speculations about thousands of deaths. These speculations were due to insufficient information of the public by the authorities and industry. Soon, we learned (see table 1) that other cyclooxygenase-2 inhibitors, such as celecoxib (Celebrex®, APC-study) and valdecoxib (Bextra® – CABG I and II-study; [1]) – when tested long enough or in risk populations – were associated with the same problem. Some journalists and "pharmacopoliticians" quickly demanded to ban all coxibs and to resort exclusively to the well-known ("approved") non-selective cyclooxygenase inhibitors. These exaggerated postulates worried the patients and annoyed many clinicians. There was no evidence that these "good old" drugs – well-known for their gastrointestinal and kidney toxicity, their ability to enhance bleedings and initiate asthma – were devoid of long-term cardiovascular toxicity as no one had ever tested them for more than a few months! Consequently it came only to the surprise of some pharmacopoliticians and journalists that even naproxen – in the USA the best selling traditional, non-selective NSAID – at low doses (200 mg/day), given for years, was also associated with an increased risk of cardiac infarction (ADAPT-study; see table 1). Considering the results of all studies on long-term use (table 1) and

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Table 1

Effect of selective and non-selective inhibitors of cyclo-oxygenase-2 on cardiovascular (CV) events in long-term trials (modified from: Medscape Cardiology 9(1), 2005. © 2005 Medscape).

Study	duration of treatment	drug/doses	indication	outcome
ADAPT	>2 years	celecoxib (400 mg/d) naproxen (400 mg/d)	M. Alzheimer	as compared to placebo: no effect with celecoxib, ~50% increase of CV-events with naproxen (events not adjudicated, preliminary results)
APC	>2 years	celecoxib (400 or 800 mg/d) vs Placebo	polyposis coli	risk increased 2.5 times (400 mg/d celecoxib) resp. 3.4 times (800 mg/d celecoxib) significant increase of CV-events afer 18 months
APPROVe	>2 years	rofecoxib (25 mg/d)	polyposis coli	termination of the study shortly before target time
CLASS	≤8 months	celecoxib (800 mg/d) diclofenac (150 mg/d) ibuprofen (2.400 mg/d)	osteoarthritis	myocardial infarction: no significant differences; low dose aspirin was permitted
TARGET	1 year	lumiracoxib (400 mg/d) ibuprofen (2.400 mg/d) naproxen (1.000 mg/d)	osteoarthritis	myocardial infarctions: lumiracoxib > naproxen lumiracoxib = ibuprofen
VIGOR	≥8 months	rofecoxib (50 mg/d) naproxen (1.000 mg/d)	rheumatoid arthritis	any thrombotic CV event, rofecoxib vs naproxen: 45 vs 19 events (p <0.002)

ADAPT: Alzheimer's Disease Anti-Inflammatory Prevention Trial, preliminary results. http://www.nih.gov/news/pr/dec2004/od-20.htm
APC: Adenoma Prevention with Celecoxib. N Engl J Med. 2005, 352.
APPROVe: Adenomatous Polyposis Prevention on Vioxx. N Engl J Med. 2005, 352.
CLASS: Celecoxib Long-Term Arthritis Safety Study. JAMA. 2000, 284(10):1247–55.
TARGET: Therapeutic Arthritis Research and Gastrointestinal Event Trial. Lancet 2004, 364(9435):665–84.
VIGOR: Vioxx Gastrointestinal Outcomes Research. N Engl J Med. 2000, 343(21):1520–30.

those of many observational studies, the FDA Advisory Panel (Feb. 2005) suggested reintroducing rofecoxib (Vioxx®) in the USA and, provided stricter warnings were given on the packages, leaving celecoxib and valdecoxib on the market [2]. The European agency (EMEA) came to similar conclusions. Obviously, there is still some merit to this class of drugs!

Coxibs are good for many patients!

Advantages of coxibs: GI, asthma, bleeding risk

Selective cyclooxygenase-2 inhibitors (coxibs) were initially developed in order to reduce the gastrointestinal toxicity of traditional NSAID's, which they do successfully (table 2)! In addition, coxibs do not increase the bleeding risk in patients with reduced blood coagulation due to diseases or drug intake, and they are not associated with aspirin inducible asthma [3].

Equality with non-selective inhibitors

With respect to kidney damage, coxibs are not worse than traditional NSAID's. Coxibs interfere with kidney function, they may increase blood pressure, and lead to fluid retention – as do traditional non-selective inhibitors. As with traditional non-steroidal, anti-inflammatory drugs, these effects are potency and dose related as well as depending on pharmacokinetic characteristics, ie more pronounced with highly active, slowly eliminated drugs (rofecoxib), as compared to those with lower effectiveness and short half-life (celecoxib; comp. [4]).

Coxibs – as all drugs – have not only class typical, but also substance specific advantages and disadvantages. The pharmacodynamic and pharmacokinetic differences have been alluded to already. In addition, allergic reactions are more pronounced in some (valdecoxib; [2]) and less pronounced in others, whilst fluid retention and increase of blood pressure are more frequently associated with the use of etoricoxib [5].

Cardiovascular effects: good, bad or bogus

Recently, the cardiovascular side effects of coxibs have drawn a lot of attention. In summary, coxibs interfere with the balance of proaggregatory (thromboxane) and antiaggregatory effects (prostacycline; [6]). It has been shown that patients at risk, eg those in need of artherosclerosis related vascular surgery, should not be treated with coxibs because of their significant prothrombotic effects (CABAG trials; [1]). However, naproxen (high dose) appears to interfere with platelet function almost as much as aspirin (low dose). A marginal cardio protective effect of naproxen is therefore likely, but this does not count for diclofenac or ibuprofen. On the other hand, coxibs are beneficial (as pointed out before) for all those who take low dose aspirin or vitamin K antagonist; the therapeutic effect of these anticoagulants remains unimpaired and does not increase the risk of bleedings – in contrast to the combination of ASA with the "traditional" NSAID ibuprofen, which may blunt the cardio-protective effect of aspirin [7]. Adding traditional NSAID's to eg phenprocoumon or warfarin increases the risk of bleedings. Consequently, many patients are better off with coxibs.

Finally, the ADAPT-study (table 1) suggests that the chronic use of all cyclooxygenase inhibitors – selective or non-selective – increases cardiovascular side effects, in particular stroke. The reason may be that the production of cardio and vascular protective prostaglandins by COX-2 is impaired equally by selective and non-selective inhibitors [8]. The observation that low dose aspirin protects, but high dose may rather enhance the cardiovascular risk in long-term studies points in the same direction [9].

New observational studies presented at the FDA hearing by David Graham (of the FDA) support the latter contention. Both, selective and non-selective cyclooxygenase-2 inhibitors, increase the risk of cardiac infarctions (most promi-

Table 2

Coxibs show less gastrointestinal (GI) toxicity than traditional NSAID's in large outcome trials. The effect is significant in EDGE, TARGET and VIGOR.

Study	duration of Treatment	drug/doses	indication	outcome
CLASS	≤8 months	celecoxib (800 mg/d) diclofenac (150 mg/d) ibuprofen (2.400 mg/d)	osteoarthritis and rheumatoid arthritis	numerically less GI lesions with Celecoxib than ibuprofen or diclofenac, not significant vs diclofenac
EDGE	up to 16.5 months	etoricoxib (90 mg/d) diclofenac (150 mg/d)	osteoarthritis	significantly less GI ADE's than with diclofenac
TARGET	1 year	lumiracoxib (400 mg/d) ibuprofen (2.400 mg/d) naproxen (1.000 mg/d)	osteoarthritis	significantly less GI lesions than with ibuprofen or naproxen
VIGOR	≥8 months	rofecoxib (50mg/d) naproxen (1.000 mg/d)	rheumatoid arthritis	significantly less GI events than with naproxen

CLASS: Celecoxib Long-Term Arthritis Safety Study, see table 1.
EDGE: Tolerability and Effectiveness of Etoricoxib. Poster, ACR San Antonio 2004 and Clin Ther. 2004, 26(1):70–83.
TARGET: Therapeutic Arthritis Research and Gastrointestinal Event Trial, see table 1.
VIGOR: Vioxx Gastrointestinal Outcomes Research, see table 1.

nent are indomethacin and meloxicam). As said before, they all interfere with the production of prostacycline, a cardio protective mediator! In conclusion, all cyclooxygenase-2 inhibitors given chronically for years appear to enhance the cardiovascular risk due to the elimination of a protective factor. It does not matter whether COX-2 inhibition is exerted by a selective or a non-selective drug. Therefore, long-term use of any cyclooxygenase inhibitor (with the notable exception of low dose aspirin) should be avoided.

Conclusion

Coxibs have significant advantages in the therapy of pain and inflammation in many, but not all patients. As all drugs they are not optimal under all conditions. They should be used cautiously, taking into account the specific pain, co-morbidity and co-medication of the individual patient. No cyclooxygenase inhibitor (with the possible exception of low dose aspirin) should be given for prolonged periods of time at analgesic doses to elderly patients. Finally, predictive laboratory tests (eg CRP, NT_proBNP, troponines and others) may help to define specific patient populations at risk, who should not take cyclooxygenase inhibitors at all or for long periods of time. For these patients we have to find other therapeutic options (work in this direction is in progress in our group and in many others; [10]).

Taking coxibs off the market would not solve the problems, but rather make pain and pain treatment more risky in many patients – and thus increase pain and suffering.

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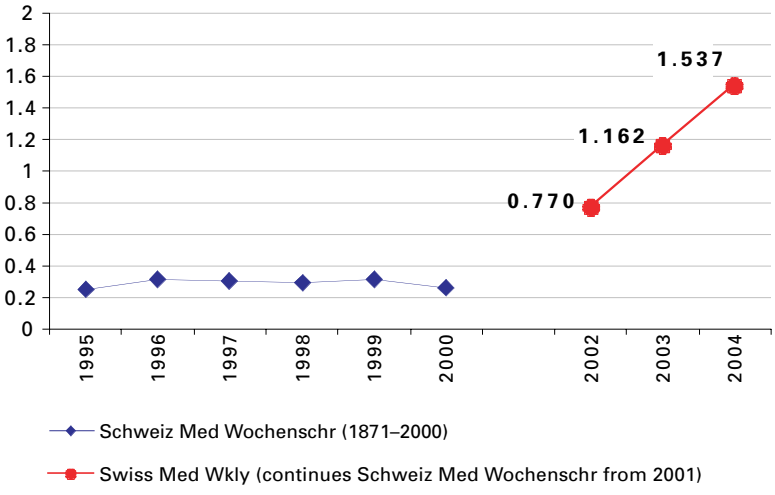

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