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COMMENTARY

Ten lessons to be learned from the withdrawal of Vioxx® (rofecoxib)

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The facts

NSAIDs are one of the most ubiquitous class of drugs, with different compounds being sold as over-the-counter drugs for a wide range of minor and major conditions. As a group, they rank first among causes of adverse drug reactions (ADRs) [1]. Severe gastrointestinal (GI) toxicity (i.e. upper GI bleeding, ulcers and perforation) due to aspirin and NSAIDs is probably the main cause of iatrogenic admission to hospitals [2], with important quantitative risk differences among NSAIDs [3–7] and with an overall attributable incidence of 150 cases/million/year [8].

In 1991, two COX-isozymes of prostaglandin G/H synthase (cyclooxigenase) were first characterized and named COX-1 (the constitutive form) and COX-2 (the inducible form). Inhibition of COX-2 was proved to be most directly implicated in reducing inflammation, whereas inhibition of COX-1 has been related to significant adverse events in the GI tract [9]. This knowledge opened the door to a new class of compounds, the selective COX-2 inhibitors, which, if proved to be safer upon the GI tract that classical NSAIDs, could be potentially important 'blockbusters' [9].

However, some words of caution are in order. First, selectivity inhibition should be regarded as a relative, rather than an absolute concept; the in vitro COX-1/COX-2 ratio differs from compound to compound (among classical as well as newer drugs); it is also critically dependent on the methodology used as well as on the concentration of the drug [9].

Secondly, NSAIDs as a group have potentially deleterious effects on the cardiovascular system; prostaglandins can counterbalance the vasoconstrictor effects of other mediators as angiotensin II, norepinephrine or vasopressin on the kidney. They can also induce the appearance of oedemas and fluid retention, cause loss of blood pressure control and increase the risk of congestive heart failure.

Thirdly, regarding its effect on platelet function, many physiopathological features of the COX-1/COX-2 equation are still evolving. The well known antiplatelet effect of aspirin is achieved by irreversible acetylation of a serine residue at position 529 in COX-1, the only isoform of the enzyme expressed in platelets, inhibiting its main metabolite (thromboxane A_2), which has proaggregant properties. Prostaglandin I_2, the predominant COX product in endothelium, has opposed effects: it inhibits platelet aggregation, causes vasodilatation and prevents the proliferation of vascular smooth-muscles. The inhibition of these effects, previously thought to be mediated by COX-1, later has been proved to be COX-2 related [10]. If this is so, strong inhibition of COX-2 dependent prostaglandin I_2 in endothelium could lead to cardiovascular damage.

In 1999, the two first anti-inflammatory drugs based upon the concept of COX-2 selectivity, the so called 'coxibs' (rofecoxib and celecoxib) were introduced into the American market. The success was impressive, and worldwide sales of rofecoxib reached US$ 2.5 billion in 2003 [11]. However, some aspects of the process were unusual. The pivotal randomised clinical trial (RCT) was only published over a year later than the commercial approval of the drug had been granted [12]. The VIGOR trial compared rofecoxib (50 mg/od) with naproxen (1.000 mg/od) in 8.076 patients with rheumatoid arthritis. The trial showed an increased number of acute myocardial infarctions (AMI) (0.4% vs. 0.1%) in patients taking rofecoxib. Concerns about the cardiovascular safety profile of the drug were initially overcome by interpreting that the results of the trial revealed more an allegedly cardioprotective effect of naproxen rather than a cardiotoxic effect of rofecoxib [12].

This hypothesis has been repeatedly questioned because, in fact, epidemiological as well as 'in vitro' data on the effect on platelet aggregation and other mechanisms related to cardiovascular safety of NSAIDs (other than aspirin) are very scarce. Regulatory authorities in USA and EU reacted by including a precautionary sentence in the labelling of marketed coxibs, reflecting the findings from the VIGOR trial. Subsequently, the coxibs 'me-too' saga increased substantially: valdecoxib, parecoxib, etoricoxib, lumiracoxib... New results from a RCT comparing lumiracoxib vs. naproxen raised more concern about an excess risk of AMI of another coxib [13].

Meanwhile, a Merck-sponsored meta-analysis of randomised trials of rofecoxib [14] and some observational studies [15–17] appeared to support the antiaggregant effect of naproxen, while other studies suggested that the increased cardiovascular risk of

rofecoxib is dose-dependent [18], and it is not shared by celecoxib [18–20].

On September 30, 2004, Merck announced the voluntary withdrawal of rofecoxib, based upon the interim analysis of the APPROVe trial (Adenomatous PolypPrevention on Vioxx). This was a Merck-sponsored RCT comparing rofecoxib (25 mg/od) vs. placebo in approximately 2.600 subjects to prevent the recurrence of colorectal polyps in individuals with a history of colorectal adenomas. After a mean follow-up of 18 months rofecoxib users had a relative risk (RR) of 2 for confirmed thrombotic events ($p = 0.007$), including cardiac as well as cerebrovascular events. These findings, and a subsequent article in the Wall Street Journal suggesting that Merck executives knew about the risk for years, made the company's stock prices to collapse [21].

The last chapter (up to November 21, 2004) of the tale is the publication in The Lancet of a so-called 'cumulative meta-analysis' of 18 RCT with rofecoxib and 11 observational studies with naproxen [22]. The authors conclude: (1) that the cardioprotective effect of naproxen exists but is small [OR: 0.86 (95% CI: 0.75–0.99)]; and (2) that the evidence about the increased risk of AMI for rofecoxib was there by the end of 2000, and that the drug 'should have been withdrawn' from the market 'several years earlier' [22]. Looking at the meta-analysis tables, two conclusions can in our view be drawn: the bigger piece of evidence is still the VIGOR study, and the reasoning based on the cardioprotective effect of naproxen cannot be ruled out. The report has been followed by the most aggressive editorial comment published up to date about the story [23].

The lessons

In our view, the most important lessons that can be learned from the process summarised above are as follows:

1. Our methodological tools to measure drugs benefit/risk ratios with precision are imperfect. RCT and observational studies are still substantially influenced by biases coming from the author's affiliation.
2. A publicly available RCT registry is urgently needed. It is the only source that can provide the public, clinicians, scientists, and policy-makers with accurate and comprehensive on line information about all the studies that are being conducted.
3. Regulatory Agencies should be truly 'independent' and transparent bodies. The pharmaceutical industry cannot be a direct source of funding for the Agencies. Strong government commitment is needed to really fulfil this requirement.
4. In the EU it is not acceptable that drug-related issues hang on the DG Enterprise, as it has been since its inception. Drugs are health tools and, as a result, their regulation should depend upon the DG of Public Health.
5. New drugs should be introduced into the market with more precautionary measures. This is specially true for 'blockbuster' drugs. Aggressive marketing of new compounds, expanding their indication away from what has been 'proved' in RCT is a dangerous exercise for everybody. The complete panorama of the positive and negative effects of a drug can only be obtained after many years of scrutiny.
6. Drug risks should always be placed in context, looking at absolute as well as relative effects. If the benefit risk/ratio of all NSAIDs is analysed in absolute terms, the conclusion can be achieved that the evidence supports that some NSAIDs are far more important causes of severe GI damage than others. This clearly justifies the withdrawal of some classical compounds. Piroxicam, for instance, has been consistently related to highly significant ORs of about 10 or 15 [3–8]. This could mean that in some markets 4% of all GI bleeding are attributable to this drug, ranking second after aspirin (unpublished data). From a public health perspective piroxicam is, at least, as dangerous as rofecoxib.
7. *Post hoc* analysis of the evidence through cumulative meta-analyses after a drug has been withdrawn from the market is unfair. Decisions about drug registration and about drug withdrawals are based upon evidence coming from many sources: information coming from '*in vitro*' or mechanism of action studies, descriptive epidemiology, case series, voluntary reporting of ADRs, data from RCT, observational studies, etc. Methodologically sound RCT are still the gold standard of clinical research; however, regulatory decisions are never based only on 'cumulative evidence' obtained through systematic reviews but, rather, based on all these heterogeneous pieces of information, which must be adequately interpreted.
8. If a cumulative meta-analysis of observational studies, like the one proposed by Jüni and coworkers [22], had been performed on the severe GI toxicity of different NSAIDs, probably several other drugs of this class should have been withdrawn from the market years ago.
9. Appropriate RCT and other designs studying the long term (1–3 years) cardiovascular effects of NSAIDs are lacking. The effects observed with rofecoxib could perhaps also be seen with other drugs, within the coxib subgroup, as well as within the classical NSAIDs.
10. The concept of a 'class effect' in pharmacology is slippery and should be used with caution. To be confident that a positive or a negative effect of a certain drug is shared with another similar drug is

not an easy task, and such an assessment requires a lot of information.

Three of the most relevant questions that remain to be properly answered are: Are the deleterious cardio- and cerebro-vascular effects seen with Vioxx applicable to other coxibs? And to other classical NSAIDs? Are these observed effects time- and dose-dependent? Other than aspirin, do any other anti-inflammatory drug have antiaggregant properties?

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