ROFECOXIB, CELECOXIB and cardiovascular events: what else has been published?

Update
October 2002

The suspicion that the use of COX-2 inhibitors is associated with a higher risk of cardiovascular events than non-selective NSAIDs, and even than placebo, continues to be a fiercely debated issue in scientific literature. In recent months, some studies, letters and editorials have gone into this matter in greater detail. Below, we briefly describe three studies that have assessed the incidence of cardiovascular events associated with the use of rofecoxib and celecoxib. The methodological problems described, however, limit the validity of these studies, leaving the doubts raised on page 5 of this Information Pack unresolved.

Rofecoxib, celecoxib and myocardial infarction

Mukherjee D, *et al. JAMA 2001;286:954-9*

- ✓ This study assessed the incidence of myocardial infarction in patients who had taken **rofecoxib** (in the VIGOR study) and **celecoxib** (in the CLASS study), using as a means of comparison the placebo group of a metanalysis on the efficacy of aspirin in primary prevention.
- ✓ *The results of this study show a higher incidence of infarction in patients taking celecoxib and rofecoxib than in those taking placebo.*
- ✓ However, the comparison with a placebo group that derives from studies with a different clinical objective (the reference populations could not be compared) is debatable).

Rofecoxib and cardiovascular events

Konstam MA et al. *Circulation* 2001;104:2280-88
Reicin A et al. *Am J Cardiol* 2002;89:204-9

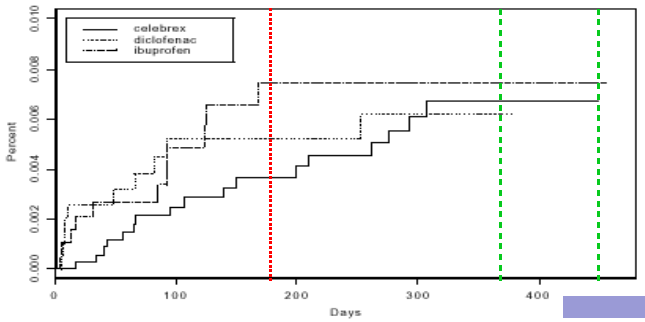
- ✓ *These two metanalyses showed that the incidence of cardiovascular events is similar in patients taking **rofecoxib** compared to non-selective NSAIDs, and that only the patients taking naproxen have a significantly lower incidence of cardiovascular events (Konstam et al).*
- ✓ To carry out these two metanalyses, no systematic review of the literature was performed (to identify all the studies available on the subject). In fact, only studies carried out by the drug-producing company were used, and their bibliographical references were not specified. It is not clear either, whether most of these studies were published in scientific journals with a review by independent experts. Both metanalyses show conflicts of interest (they were funded by the company producing rofecoxib).
- ✓ The results obtained are therefore not conclusive with regards to the cardiovascular safety of rofecoxib, in that they were obtained from selected studies and not from all the studies available.

CELECOXIB and gastrointestinal risks: what else has been published?

The gastrointestinal safety of COX-2 inhibitors continues to be a fiercely debated subject in scientific literature, and in recent months, some studies, letters and editorials have gone into this matter in greater detail. Below, we briefly describe methods and results of a systematic review of randomised controlled studies published in the *British Medical Journal* on 21st September 2002 (Deeks JJ *et al. BMJ* 2002;325:619-26) which, other than the efficacy of the drugs, discusses the incidence of gastrointestinal events (both complicated and non-complicated) associated with the use of *celecoxib compared to non-selective NSAIDs* in patients with rheumatoid arthritis or osteoarthritis. The results of this work do not substantially alter the conclusions of the FDA on the CLASS study (shown on page 4 of ths Information Pack).

What we already knew from the FDA

Complicated ulcers after 6-12 months (clinical diagnosis)



As shown in the above figure (from the FDA report available on the website: http://www.fda.gov/ohrms/dockets/ac/01/briefing/3677b1_04_stats.pdf), the differences between celecoxib, ibuprofen and diclofenac in complicated ulcers in the CLASS study are at their highest in the sixth month (results published in *JAMA* – red line) and are notably reduced in the subsequent months, as already stated on page 4 of this Information Pack. The FDA analysis states that the differences between the drugs at 6, 12 and 15 months (the latter two, marked with green lines, are the only ones set out in the study protocol) are not statistically significant.

What the Deeks *et al* (*BMJ* 2002;325:619-26) study does NOT add to our knowledge

- ✓ The authors reported the CLASS study data (in which 7968 patients took part) on the incidence of symptomatic ulcers + complicated ulcers in patients who took celecoxib, ibuprofen or diclofenac.
- ✓ The data relative to complicated ulcers (excluding symptomatic ulcers) were not reported. Complicated ulcers were the main indicator of the CLASS study, as shown in the study protocol.
- ✓ The results presented are those relative to the first six months of the study (already shown on page 4 of this Information Pack). This choice was made despite the FDA having published *complete* data of the study (length: 12-15 months). Much criticism was levelled at the authors of the CLASS study through letters and editorials[1,2,3], since the analysis at six months was not set out in the study protocol. It must be noted that the Deeks *et al* study has conflicts of interest (having been funded and carried out by the company producing celecoxib).

Other parameters taken into consideration in the Deeks *et al* study: endoscopic (NON-clinical) ulcers at 3 months

- ✓ The authors performed a metanalysis, combining the results of 5 randomised controlled studies (for a total of 2742 participants), that compared the incidence of ulcers in patients who had taken celecoxib or non-selective NSAIDs - ibuprofen, naproxen or diclofenac - for approximately 3 months at the most (12 weeks).
- ✓ The incidence of ulcers (shown endoscopically) was lower in patients who had taken celecoxib compared to non-selective NSAIDs (RR = 0.29; 95% CI 0.21-0.41).
- ✓ These data contradict the data of the CLASS study (7968 patients) published by the FDA, on clinical ulcers at 6 and 12 months — see above box. Still to be assessed is the clinical relevance of endoscopic ulcers (study of Deeks *et al*) compared to clinically diagnosed ulcers (CLASS study/FDA data), and the period of use (3 months compared to 6-12 months).

Gastric perforation caused by COX-2 inhibitors in acute cases: what should be clarified?

- ✓ Regional prescription data show that, in Italy, COX-2 inhibitors are predominantly used in acute cases[4].
- ✓ There are no reliable data (from randomised studies of large sample sizes or from metanalyses) that demonstrate that using COX-2 inhibitors instead of non-selective NSAIDs in acute cases reduces the incidence of gastrointestinal ulcers.
- ✓ Therefore, it is not clear whether COX-2 inhibitors have advantages over non-selective NSAIDs when used in acute cases.

1 Drug Information Bulletin 2001, No. 6:224-6
2 Juni P *et al. BMJ* 2002;324:1287-8
3 Budenholzer BR *et al. BMJ* 2002;325:161-4
4 http://www.ben.iss.it/pre_2002/giugno02/1.htm