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Randomized Controlled Trials of COX-2 Inhibitors

An Analysis of Doses Used and Trends Over Time to Investigate Implications for Comparative Safety

Gudrun Stefansdottir,[1,2] *Marie L. De Bruin,*[1,2,3] *Mirjam J. Knol,*[1,2] *Diederick E. Grobbee*[1] and *Hubert G.M. Leufkens*[2,3]

1 Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht, the Netherlands
2 Division of Pharmacoepidemiology and Pharmacotherapy, Utrecht Institute for Pharmaceutical Sciences, Utrecht, the Netherlands
3 Medicines Evaluation Board, The Hague, the Netherlands

Abstract

Background: Naproxen, ibuprofen and diclofenac are frequently used as comparators in randomized controlled trials (RCTs) on the safety and efficacy of cyclooxygenase (COX)-2 inhibitors. Different comparator doses may influence the results of RCTs. It has been hypothesized that RCTs of COX-2 inhibitors where different doses were administered resulted in different conclusions about the cardiovascular safety of COX-2 inhibitors. High comparator doses may let COX-2 inhibitors look better in terms of safety, while low comparator doses may result in the opposite.

Objective: The aim of the study was to compare doses of COX-2 inhibitors and comparator drugs used in RCTs, and to investigate dose changes over time.

Study Design and Methods: We searched the Cochrane Central Register of Controlled Trials, The Cochrane Library for published Cochrane reviews, Clinicaltrials.gov and PubMed, for RCTs between 1995 and 2009 in which celecoxib or rofecoxib were compared with naproxen, ibuprofen or diclofenac. All articles labelled as RCTs mentioning rofecoxib or celecoxib and one or more of the comparator drugs in the title and/or abstract were included. We extracted information on doses of both non-selective NSAIDs and selective COX-2 inhibitors used in the RCTs, and study year. The Mann-Whitney test was used to compare the difference in median dose in rofecoxib and celecoxib RCTs. Linear regression was performed to evaluate trends in dosage over time. For comparisons between COX-2-inhibitors, celecoxib trials after the 2004 market withdrawal of rofecoxib were excluded.

Results: Median defined daily dose (DDD) of celecoxib (2.00) was higher than the median DDD of rofecoxib (1.00; $p < 0.001$), whereas non-selective NSAID doses were comparable in rofecoxib (2.00) and celecoxib (2.00; $p = 0.988$) studies. In both groups, the non-selective NSAID doses decreased over time

(B [regression coefficient] = –0.07; p = 0.28, and B = –0.054; p = 0.09, respectively). In contrast, the DDDs of rofecoxib increased slightly over time (B = 0.037; p = 0.28), whereas the celecoxib DDDs decreased over time (B = –0.081; p = 0.09). In due course, the contrasts between DDDs of COX-2 inhibitors and non-selective NSAIDs converged, both in rofecoxib and celecoxib RCTs; therefore, doses have become more comparable in recent years because of differences in steepness of two decreasing dose trends in the case of celecoxib, and opposing dose trends in the case of rofecoxib.

Conclusions: Although the dose trends over time differed for RCTs comparing rofecoxib and celecoxib with diclofenac, ibuprofen or naproxen, the results of our study do not support the hypothesis that dose trends influenced the decision to continue marketing celecoxib after the withdrawal of rofecoxib because the overall median DDD of celecoxib was substantially higher than the median DDD of rofecoxib, while non-selective NSAID DDDs were comparable.

Background

Rofecoxib and celecoxib, two highly publicized cyclooxygenase (COX)-2 inhibitors, were marketed in the 1990s. They are indicated for the treatment of the symptoms of osteoarthritis and rheumatoid arthritis, acute pain and primary dysmenorrhoea. It was expected that they would cause fewer gastrointestinal problems than non-selective NSAIDs and therefore be safer for patients.

Results from the VIGOR (Vioxx GI Outcomes Research) trial comparing rofecoxib 50 mg/day with naproxen 500 mg twice daily showed a higher incidence of myocardial infarction (MI) in patients using rofecoxib compared with patients using naproxen. The conclusion was that the significantly lower incidence of MI in the naproxen group compared with the rofecoxib group was due to possible cardioprotective effects of naproxen, and not associated with high doses of rofecoxib.[1] The Advantage trial studied the gastrointestinal tolerability and effectiveness of rofecoxib 25 mg daily compared with naproxen 1000 mg daily. In this study there was not a significant difference between the incidence of MI in the two groups, while in the naproxen group the incidence of strokes was significantly higher compared with the rofecoxib group.[2] In the end, evidence of a higher risk of MI in patients using rofecoxib in the APPROVE (The Adenomatous Polyp Prevention on Vioxx) trial, a randomized controlled trial (RCT) in which rofecoxib (25 mg) was compared with placebo, led to the worldwide marketing withdrawal of rofecoxib by the marketing authorization holder in September 2004.[3,4]

This led to further discussion regarding the safety of COX-2 inhibitors. The US FDA and the European Medicines Agency (EMA) requested further information on all COX-2 inhibitors that remained on the market, and an assessment of their safety.[5,6] The current hypothesis on the underlying mechanism of cardiovascular effects of COX-2 inhibitors is that they selectively inhibit prostacyclin (PGI_2) production but do not block thromboxane A_2 (TXA_2). This leads to an imbalance of TXA_2 and PGI_2 that may influence the risk of thrombotic events in predisposed patients. The FDA and EMA consider cardiovascular effects to be dose-related class effects of COX-2 inhibitors;[5-7] however, non-selective NSAIDs also increase the risk of cardiovascular disease.[8-10] This is considered to be mediated by an increase in systolic blood pressure.[11,12] On the other hand, aspirin (acetylsalicylic acid) use lowers mortality from ischaemic heart disease, and it has been hypothesized that naproxen may also have cardioprotective effects but data are inconclusive.[7,13-15]

Celecoxib was not withdrawn from the market, although new contraindications and warnings were issued after evaluation of all available

data by the EMA and FDA. The new contraindications included warnings about prescribing COX-2 inhibitors to patients with risk factors for heart disease or ischaemic heart disease and/or cerebrovascular disease.[5,16,17] At the time of evaluation, available safety data on celecoxib included results from the APC (Adenoma Prevention with Celecoxib) and PreSAp (The Prevention of Colorectal Sporadic Adenomatous Polyps) RCTs.[18,19] The APC trial, a clinical trial comparing celecoxib 200 and 400 mg twice daily with placebo for the prevention of colorectal adenoma, showed an increased risk of cardiovascular events, including death from cardiovascular causes in the celecoxib groups. The absolute risk was higher in patients with a history of cardiovascular events at baseline. Furthermore, a dose-related association between celecoxib use and death from cardiovascular causes was observed.[18] An interim analysis of the PreSAP trial comparing celecoxib 400 mg once daily with placebo did not find any statistically significant increase in cardiovascular events; however, the study was terminated prematurely because of the findings of the APC trial.[19]

It has been hypothesized that RCTs of COX-2 inhibitors where different doses of study and comparator drug were administered have resulted in different conclusions about the cardiovascular safety of COX-2 inhibitors.[20] High comparator doses may let COX-2 inhibitors look better in terms of cardiovascular safety, while low comparator doses may result in the opposite. To our knowledge, no-one has systematically reviewed RCTs in order to support this hypothesis.

The objective of our study was to investigate the doses of COX-2 inhibitors and comparator drugs in RCTs and to address the question of whether the dose dynamics were differential between individual drugs over time. Because celecoxib still remains on the market, we expected to see lower doses of celecoxib than rofecoxib and higher comparator doses in celecoxib RCTs compared with rofecoxib RCTs. Moreover, it was expected that rofecoxib and celecoxib doses would decrease over time when information from postmarketing surveillance about possible cardiovascular risks accumulated.

Methods

Data Sources and Searches

We searched the Cochrane Central Register of Controlled Trials, Clinicaltrials.gov and Pubmed for RCTs that were carried out between January 1995 and December 2009 in which celecoxib or rofecoxib were compared with naproxen, ibuprofen and/or diclofenac, among patients aged 18 years and older. To check the completeness of our search we searched the Cochrane Library for published Cochrane reviews for any RCTs that were missing from our search. One additional RCT was found in a Cochrane review that was added to our study. All articles labelled as RCTs that mentioned the names of rofecoxib or celecoxib and one or more of the comparator drugs in the title and/or abstract were searched. To be eligible for our study, information about the doses of both COX-2 inhibitor and comparator drugs had to be available. None of the identified studies had missing information on dose. Studies that estimated pain relief and time to re-medication after a single dose postsurgery were excluded as the aim of these studies was to estimate the time until the patient asks for additional dose and patients are not exposed to a predefined constant dose. For a complete overview of the included studies see appendix A (Supplemental Digital Content 1, http://links.adisonline.com/DSZ/A50).

Data Extraction

We extracted information on the doses (mg/day) of both non-selective NSAIDs and COX-2 inhibitors that were used in the RCTs, as well as the study year. The WHO definition on defined daily doses (DDDs) was used to standardize the study doses by dividing the dose in mg/day with the DDD in order to make the different drugs comparable. The Nordic Council on Medicines (NLN) in collaboration with Norwegian researchers developed the Anatomical Therapeutic Chemical (ATC)/DDD system as a unit of measurement. Since 1981, the WHO has recommended the use of this system in international drug utilization studies. The definition of a DDD is the assumed

average maintenance dose per day for a drug when used for its main indication in adults.[21]

Study year was defined as the year when the study started. In those cases where the start date of an RCT was not available, we contacted the corresponding author of the trial for this information.

Hence, we combined the study dose of all non-selective NSAIDs that were used in rofecoxib trials and all non-selective NSAIDs used in celecoxib trials to see the overall change in comparator dose over time.

Data Analysis

Single-regression imputation where random error was taken into account was used to impute study year for the 35 (45%) studies where it was not possible to retrieve the start date from the publication or by contacting authors. The imputation was based on publication date and the duration of study with the limitation that rofecoxib RCTs could not start after the 2004 marketing withdrawal. Because the dose-differences (Coxib DDD – NSAID DDD) were not normally distributed, the Mann-Whitney test was used to compare the DDD differences of rofecoxib and celecoxib versus the three non-selective NSAIDs. To evaluate the trends in dose over time for comparison of rofecoxib and celecoxib with DDDs of all non-selective NSAIDs combined, linear regression based on the number of studies was used. When comparing rofecoxib and celecoxib trials, we excluded celecoxib trials that were carried out after the 2004 market withdrawal of rofecoxib. The unit of analysis was comparisons within the RCTs; one RCT could therefore contribute to more than one comparison if multiple drugs or doses were compared. All statistical analyses were carried out using SPSS 16.0 for Windows (SPSS Inc., Chicago, IL, USA).

Results

We included 77 RCTs in which 120 active control comparisons between the non-selective NSAIDs and COX-2 inhibitors were made. Up until 2004, we found 106 comparisons between the non-selective NSAIDs and COX-2 inhibitors in 70 RCTs. Naproxen was the most commonly used comparator drug, used in 48% of all comparisons. All comparator NSAIDs were prescribed through-

Table I. General characteristics of randomized controlled trials (RCTs) in which celecoxib or rofecoxib were compared with naproxen, ibuprofen or diclofenac (1995–2009)

RCT characteristics	Rofecoxib	Celecoxib
Total number of comparisons (%)[a]	50 (100)	70 (100)
Mean study start year (SD, min., max.)	1999 (2.3, 1996, 2004)	2002 (3.4, 1996, 2009)
Mean study duration [wk (SD, min., max.)]	10.7 (15.4, 0.5, 52)	18.2 (27.5, 0.5, 144)
Study purpose [n (%)]		
pharmacology	16 (32)	14 (20)
efficacy: pain relief	19 (38)	34 (49)
safety: GI tolerability/cardiovascular	14 (28)	20 (28)
other	1 (2)	2 (3)
NSAID comparator		
naproxen	19 (38)	39 (56)
ibuprofen	16 (32)	15 (21)
diclofenac	15 (30)	16 (23)
Mean number of participants (SD, min., max.)	611 (1374, 24, 8076)	3672 (6732, 13, 20 000)
Mean age of participants [y (SD, min., max.)][b]	49.2 (17.8, 22.8, 73.8)	51.7 (14.0, 21.5, 74.0)

a 29 RCTs with rofecoxib, 43 with celecoxib, 5 with both rofecoxib and celecoxib; one RCT may contribute more than one comparison (see appendix A, Supplemental Digital Content 1).

b Information on mean age of patients was missing in 44 of 120 comparisons.

GI = gastrointestinal; **max.** = maximum; **min.** = minimum.

out the period from 1995 to 2009. Table I shows the general characteristics of the comparisons.

The prescribed doses varied between 12.5 mg and 50 mg (0.50–2.00 DDDs) of rofecoxib and between 100 mg and 1200 mg (0.50–6.0 DDDs) of celecoxib. Overall, the dose of rofecoxib (median 1.00 DDD) was significantly lower than the celecoxib dose (median 2.00 DDDs; p Mann-Whitney <0.001). In the same period, the median DDD of NSAID comparators in both rofecoxib and celecoxib RCTs were the same (2.00 DDDs).

Table II shows the median DDDs of rofecoxib and celecoxib comparisons according to each NSAID used in the period 1995–2004. The median DDD of celecoxib did not vary between different NSAID comparators (2.00 vs naproxen, 2.00 vs ibuprofen, 2.00 vs diclofenac), and likewise for rofecoxib (1.00 vs naproxen, 1.00 vs ibuprofen, 1.00 vs diclofenac). On the other hand, the median NSAID dose according to COX-2 inhibitor showed more variety; median naproxen dose was the same in rofecoxib and celecoxib trials (2.00 DDDs). The same was true for diclofenac (1.50 DDDs), whereas median ibuprofen DDD was higher in rofecoxib trials (2.00 vs 1.50 DDDs, respectively). In all three NSAID groups, the median DDD of rofecoxib was lower than the comparator, whereas the median celecoxib DDD was equal to the comparator in naproxen RCTs and higher in ibuprofen and diclofenac RCTs.

Figure 1 depicts the changes in DDDs of both COX-2 inhibitor and non-selective NSAID comparators over time according to COX-2 inhibitor. In both groups, the non-selective NSAID doses decreased over time {figure 1a: B (regression coefficient from linear regression analysis [ANOVA]) = –0.070; p = 0.003; figure 1b: B = –0.054; p = 0.004}. In contrast, the DDDs of rofecoxib (which were lower than the non-selective NSAID comparators) slightly increased over time (figure 1a: B = 0.037; p = 0.28), whereas the celecoxib DDDs (which were higher than the non-selective NSAID comparators) decreased over time, together with the decreasing non-selective NSAIDs (figure 1b: B = –0.081; p = 0.09). Looking at the contrasts between DDDs of COX-2 inhibitors and non-selective NSAIDs over time, the doses of both rofecoxib and celecoxib converged with those of non-selective NSAID doses and became more comparable in recent years because of differences in steepness of two decreasing dose trends in the case of celecoxib, and opposing dose trends in the case of rofecoxib.

This trend towards more equal comparisons was confirmed by looking at the celecoxib trials performed after 2004. In this period we identified seven RCTs, with a total of 14 different comparisons. Naproxen was the most common comparator (n = 6), while ibuprofen and diclofenac were used in four comparisons each. Median celecoxib DDD was 1.50 (min. 1.00, max. 2.00) and, likewise, the median NSAID DDD was 1.50 (min. 0.75, max. 2.00). DDDs of celecoxib and comparator drugs were lower than in celecoxib trials

Table II. Median defined daily dose (DDD) of cyclooxygenase (COX)-2 inhibitor and non-selective NSAID for each comparison between celecoxib or rofecoxib and naproxen, ibuprofen or diclofenac (1995–2004) and median DDD difference[a]

Comparisons	N	COX-2 inhibitor		NSAID		p-Value[b]
		median dose [mg (min., max.)]	median DDD (min., max.)	median dose [mg (min., max.)]	median DDD (min., max.)	
Rofecoxib vs naproxen	19	25 (12.5, 50)	1.00 (0.50, 2.00)	1000 (440, 1100)	2.00 (0.88, 2.20)	0.16
Celecoxib vs naproxen	33	400 (100, 1200)	2.00 (0.50, 6.00)	1000 (440, 1000)	2.00 (0.88, 2.00)	
Rofecoxib vs ibuprofen	16	25 (12.5, 50)	1.00 (0.50, 2.00)	2400 (800, 2400)	2.00 (0.67, 2.00)	0.001
Celecoxib vs ibuprofen	11	400 (200, 800)	2.00 (1.00, 4.00)	1800 (1200, 2400)	1.50 (1.00, 2.00)	
Rofecoxib vs diclofenac	15	25 (12.5, 50)	1.00 (0.50, 2.00)	150 (100, 150)	1.50 (1.00, 1.50)	0.03
Celecoxib vs diclofenac	12	400 (200, 800)	2.00 (1.00, 4.00)	150 (100, 150)	1.50 (1.00, 1.50)	

a DDD: rofecoxib = 25 mg, celecoxib = 200 mg, naproxen = 500 mg, ibuprofen = 1200 mg, diclofenac = 100 mg.

b Dose differences (Coxib DDD–NSAID DDD) between rofecoxib and celecoxib trials.

max. = maximum; **min.** = minimum.

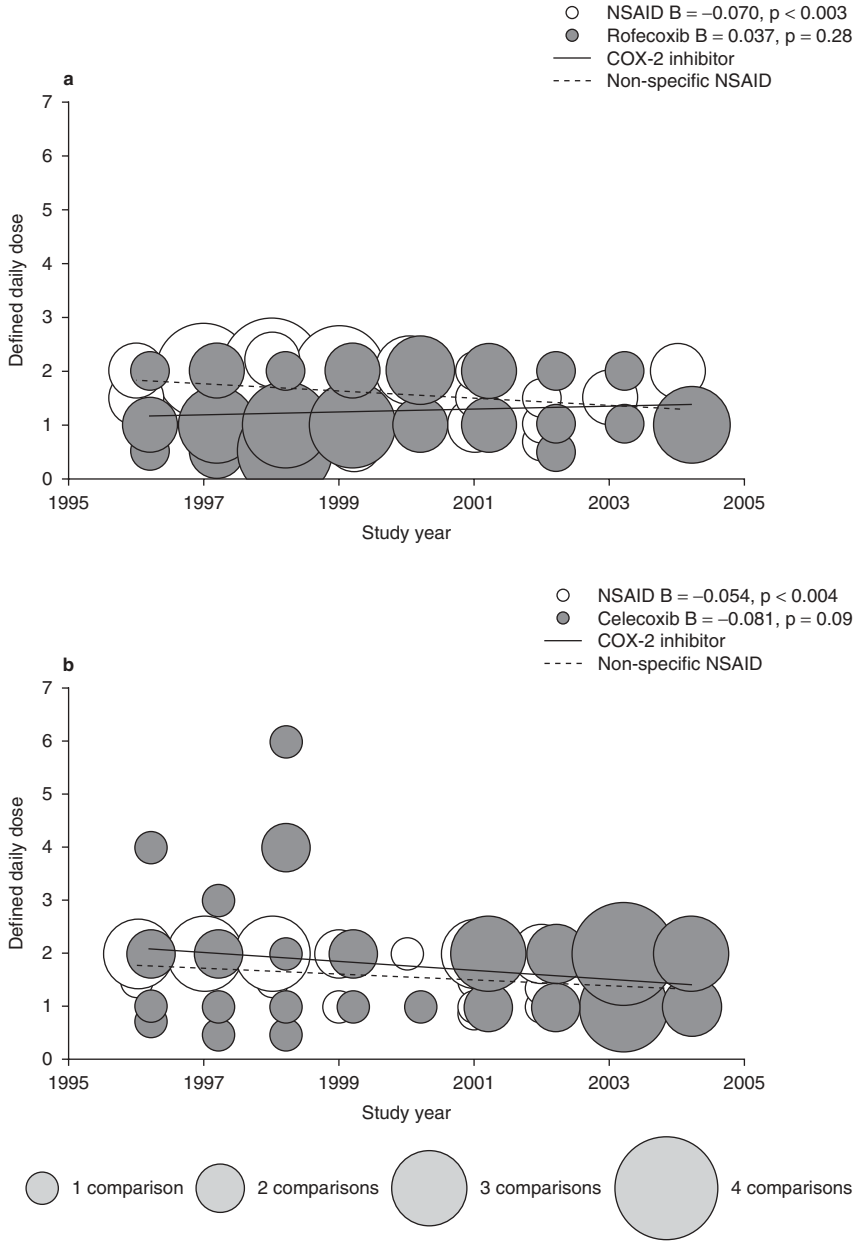

Fig. 1. (**a**) Defined daily doses (DDDs) of NSAIDs and rofecoxib; (**b**) DDDs of NSAIDs and celecoxib. **B** = the unstandardized regression coefficient. **COX** = cyclooxygenase.

before 2005 (p = 0.43 and p = 0.06, respectively). In the period 2005–9, the mean celecoxib dose further decreased (B = –0.200; p = 0.11), while NSAID doses remained stable (B = 0.007; p = 0.96).

The study by Leese et al.,[22] which compared the effects of celecoxib and naproxen on platelet function in healthy adults, showed unusually high celecoxib doses (1200 mg/day, six DDDs).

Table III. Regression coefficients and median doses of cyclooxygenase (COX)-2 inhibitors and all NSAIDs combined, for all randomized controlled trials and subgroups (1995–2004)

Drug administration details	N	Median defined daily dose			Time trend 1995–2004			
		coxib	NSAID	dose difference	B coxib	p-value	B NSAID	p-value
Rofecoxib, overall	50	1.00	2.00	−1.00	+0.037	0.28	−0.070	0.003
<500 patients	30	1.00	2.00	−1.00	+0.015	0.75	−0.078	0.03
≥500 patients	20	1.00	1.50	−0.50	+0.026	0.81	+0.075	0.08
<12 wk	35	1.00	2.00	−1.00	+0.052	0.22	−0.093	0.001
≥12 wk	15	1.00	2.00	−1.00	+0.027	0.74	−0.017	0.77
Celecoxib, overall	56	2.00	2.00	−0.00	−0.081	0.09	−0.054	0.003
<500 patients	35	2.00	1.75	+0.25	−0.109	0.15	−0.066	0.03
≥500 patients	21	2.00	2.00	±0.00	−0.085	0.30	−0.039	0.18
<12 wk	28	2.00	2.00	±0.00	−0.211	0.02	−0.066	0.11
≥12 wk	28	1.50	2.00	−0.50	−0.068	0.28	−0.039	0.03

B = regression coefficient from linear regression analysis (ANOVA).

To estimate the effect of this study on the decrease in celecoxib dose over time we excluded this dose from a linear regression of all other celecoxib study doses. By excluding this study, the decrease in celecoxib dose over time became less steep ($B = -0.052$; $p = 0.19$ vs $B = -0.081$; $p = 0.19$).

In a subgroup analysis of RCTs smaller than 500 patients, RCTs with 500 patients or more and a duration of <12 weeks or 12 weeks or longer, we see similar trends as for all RCTs. Rofecoxib doses remain stable, and trends are, overall, the same except in the subgroup of trials with over 500 patients where non-selective NSAIDs show a non-significant increase over time. The DDDs of celecoxib and non-selective NSAIDs show a negative trend over time. Table III shows regression coefficients and median doses of COX-2 inhibitors and non-selective NSAIDs for all studies and the subgroup analysis.

Discussion

Over time, dose contrasts between rofecoxib and non-selective NSAIDs decreased because of a trend towards an increase in rofecoxib dose and a decrease in non-selective NSAID dose. In celecoxib RCTs the time trend was towards lower celecoxib doses; however, the contrast between doses was not as great as in rofecoxib trials. Despite this time trend, the difference between median doses of the different non-selective NSAID comparators and rofecoxib were considerably greater than observed differences in celecoxib RCTs; therefore, it is unlikely that dose changes over time could have contributed to a differential weighting of the comparative cardiovascular risk of the two drugs because DDDs of rofecoxib were significantly lower than DDDs of celecoxib.

In a systematic review of observational studies of non-selective NSAIDs and COX-2 inhibitors, McGettigan and Henry[23] found that cardiovascular risk of rofecoxib was dose-dependent and that it was not possible to exclude increased cardiovascular risk associated with celecoxib use in doses above 200 mg/day. In his review, Howes[24] came to the same conclusion about celecoxib.

Another systematic review of NSAIDs and the risk of myocardial infarction by Scott et al.[25] concluded that the risk of most NSAIDs was greatest when given in high doses for prolonged periods of time. This supports our theory that when lower doses are used in RCTs the results will show a reduced risk of cardiovascular events. This means that there should have been a higher chance of adverse effects in the celecoxib RCTs where the median DDDs were higher overall than in the rofecoxib RCTs, if the risk of adverse effects from the two drugs was the same. However, studies from daily practice have reported 200 mg/day to be the most commonly prescribed dose of celecoxib.[26,27] This dose does not reflect RCT doses, where we found the median dose to be 400 mg/day. This could result in less safety issues in daily practice compared with the RCTs.

For rofecoxib, a dose of 12.5 mg/day was reported as the most common dose in daily practice in the UK compared with 25 mg/day in the US.[26,27] Consequently, there could be a difference in cardiovascular risk in these two populations.[28,29] Differences between prescribing patterns and RCT doses can explain the difference between cardiovascular risk that was found in epidemiological studies and RCTs.[3,29]

Length of COX-2 inhibitor treatment has been mentioned in the context of the cardiovascular risk of these drugs. Lee et al.[30] stated that most of the earlier RCTs of celecoxib were short-term trials and therefore did not appear to show any increase in cardiovascular risk. In our present study, we did not assess in detail the effects of study duration; however, the mean length of the celecoxib trials studied was comparable with the mean length of rofecoxib trials in the period 1995–2005 (10.5 weeks and 10.7 weeks, respectively; $p = 0.95$). In addition, the dose time trends in studies of at least 12 weeks were comparable with the overall time trends, except for the less steep decrease in NSAID dose in long-term rofecoxib RCTs (see table III).

Previous studies on other drug classes have shown that the issue of dose in RCTs is very important. This was, for example, the case with haloperidol. In a study by Hugenholtz et al.[31] RCTs of atypical antipsychotics in schizophrenia where haloperidol was used as a comparator drug were studied. They found that in over 90% of the RCTs haloperidol was used in doses that were higher than the upper limit of the officially recommended doses for haloperidol. This could cause more adverse effects of haloperidol in those RCTs and more favourable results for the study drug. However, they found that RCT doses of haloperidol were reduced over time.

All non-selective NSAIDs were used from the time of the first study until 2009; therefore, the safety profile of the non-selective NSAIDs does not seem to affect the choice of comparator drug in the RCTs. It has been suggested that naproxen is cardioprotective, which would make the COX-2 inhibitor look worse in comparison in terms of cardiovascular risk but this does not seem to have influenced the decision to use naproxen as a comparator drug in rofecoxib or celecoxib RCTs.

When interpreting the results of this study, certain limitations should be taken into account. The databases we searched for RCTs did not have complete data available for year of start of the study. We tried to contact the corresponding authors of the studies for additional information; however, start date could not be retreived for 35 of the 77 studies. To solve this problem, we therefore imputed the start date taking random error into account.

Previously, others have related COX-2 potency to the cardiovascular risk of NSAIDs. Based on current information it was not possible to calculate the COX-2 potency for different doses of COX-2 inhibitors and the comparator non-selective NSAIDs. We therefore decided to use the definition of DDDs, which is also based on the efficacy of the drug, to standardize the study doses. The percentage inhibition of COX-2 receptors for one DDD of the study drugs ranged from 75% for ibuprofen to 100% for diclofenac in the study by García Rodríguez et al.[32] The COX-2 inhibiton of rofecoxib and celecoxib was similar (90 and 86%, respectively). COX-2 inhibiton of 1.5 DDDs of naproxen was 95%.[32] In future studies, it may be interesting to combine the information on dose and potency.

When evaluating the safety of COX-2 inhibitors, the regulatory authorities also based their decisions on placebo-controlled trials, without an active comparator. The APPROVE trial that lead to the voluntary marketing withdrawal of rofecoxib was a placebo-controlled trial. A recent pooled analysis of placebo-controlled rofecoxib trials by Ross et al.[33] showed that cardiovascular risk could have been detected earlier if such an analysis had been carried out as soon as new data emerged. Our study was restricted to RCTs that compared COX-2 inhibitors with active non-selective NSAID controls. About half of the studies included an additional placebo arm (56/120 comparisons). The median dose of rofecoxib was 1.00 DDD in both placebo-armed studies and studies with only active controls (min. 0.50, max. 2.00 for both). For celecoxib, the median dose was 2.00 DDDs in both placebo-armed and active control studies (min. 0.50, max. 6.00 and min. 1.00, max. 4.00, respectively).

Our study raises the issue of how regulators should interpret safety-related data. The EMA and FDA have no guidelines on choice of comparator drug or comparator dose in COX-2 inhibitor RCTs. Making guidelines on which comparator to use and in which dose can make the results from different RCTs more comparable and therefore make regulatory decisions easier.

In the seven RCTs (14 comparisons) that were carried out on celecoxib after the withdrawal of rofecoxib we found lower DDDs of celecoxib than in trials carried out before 2004. During this period there was also a trend for a further decrease in dose. This could be due to the extensive discussion about safety of COX-2 inhibitors and re-evaluation of what is a safe and effective dose.

Conclusions

The difference in median DDD between the COX-2 inhibitor and comparator was higher in rofecoxib RCTs than in celecoxib RCTs when naproxen and ibuprofen were the comparators. This was due to lower median DDD of rofecoxib than celecoxib. Only in celecoxib trials did we see COX-2 inhibitor doses that were higher than those of the comparator. Overall, doses of rofecoxib increased while doses of non-selective NSAIDs decreased over time; therefore, the contrast between the doses decreased over time. Doses of celecoxib decreased more over time than doses of comparator non-selective NSAIDs. In the case of rofecoxib and celecoxib, it is unlikely that these trends over time may have influenced the decision to keep celecoxib on the market after the withdrawal of rofecoxib. Median DDDs of celecoxib were higher than median DDDs of rofecoxib and should therefore have shown a higher cardiovascular risk if the risk of the two drugs was the same per DDD. Lower doses that were seen in later trials suggest that investigators took into account knowledge about risks from previous trials by lowering the doses in later trials.

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Correspondence: Dr *Marie L. De Bruin*, Division of Pharmacoepidemiology and Pharmacotherapy, Utrecht Institute for Pharmaceutical Sciences, PO Box 80082, 3508 TB Utrecht, the Netherlands.
E-mail: m.l.debruin@uu.nl