ORIGINAL RESEARCH ARTICLE

Drug Safety 2005; 28 (5): 435-442
0114-5916/05/0005-0435/$34.95/0

© 2005 Adis Data Information BV. All rights reserved.

Incidence of Thrombotic Cardiovascular Events in Patients Taking Celecoxib Compared with Those Taking Rofecoxib

Interim Results from the New Zealand Intensive Medicines Monitoring Programme

Mira Harrison-Woolrych,[1] *Peter Herbison*,[2] *Rachael McLean*,[1] *Janelle Ashton*[1] and *Jim Slattery*[3]

1 Intensive Medicines Monitoring Programme, Department of Preventive and Social Medicine, University of Otago, Dunedin, New Zealand
2 Department of Preventive and Social Medicine, University of Otago, Dunedin, New Zealand
3 European Medicines Evaluation Agency, Westferry Circus, Canary Wharf, London, UK

Abstract

Background: Rofecoxib was withdrawn from the market worldwide because of concerns relating to cardiovascular safety. There is conflicting evidence as to whether celecoxib, the most popular alternative to rofecoxib, carries the same cardiovascular risks. This study's aim was to compare the incidence of thrombotic cardiovascular events in patients taking celecoxib with patients taking rofecoxib.
Methods: Prescription event monitoring methodology was used in this prospective, longitudinal, observational cohort study, in which cohorts of patients were established from prescription data and thrombotic cardiovascular events were identified from follow-up questionnaires to patients' doctors and other sources.
Subjects: New Zealand patients with at least one prescription for either rofecoxib or celecoxib between 1 December 2000 and 30 November 2001.
Analysis: For this interim analysis the total cohorts were separated into three groups at different stages of follow-up: complete, incomplete and no follow-up. Cox's proportional hazards models were applied to calculate hazard ratios for celecoxib compared with rofecoxib.
Results: The total cohorts included 26 403 patients receiving rofecoxib and 32 446 patients receiving celecoxib. 4882 (18%) rofecoxib and 6267 (19%) celecoxib patients had been completely followed up. In this group the unadjusted hazard ratio for celecoxib compared with rofecoxib was 1.07 (95% CI 0.59, 1.93). After adjustment for age this hazard ratio was 0.94 (95% CI 0.51, 1.70). Further adjustment for sex, 'as required' use, indication for use, concomitant NSAID use and pre-existing cardiovascular disease resulted in only minor changes to the hazard ratio.
Conclusion: This interim analysis of the Intensive Medicines Monitoring Programme data suggests that in 'real-life' postmarketing use in New Zealand there is no significant difference in the risk of cardiovascular thrombotic events in patients taking celecoxib compared with those taking rofecoxib.

Background

In October 2004, rofecoxib (Vioxx® [1]) was withdrawn from the worldwide pharmaceutical market when the market authorisation holder for rofecoxib acknowledged that this medicine carried serious cardiovascular risks.[1] The company's decision was based on information from the APPROVe (Adenomatous Polyp Prevention on Vioxx®) study, a randomised placebo-controlled trial that demonstrated an almost 2-fold increased risk of thrombotic cardiovascular events in patients receiving rofecoxib compared with placebo.[2]

The withdrawal of rofecoxib raised the question of whether other cyclo-oxygenase (COX)-2 inhibitors have the same increased risk of thrombotic cardiovascular events. The APC (Adenoma Prevention with Celecoxib) trial, published in February 2005, demonstrated an increased risk of major fatal or non-fatal cardiovascular events in patients taking celecoxib compared with placebo.[3] However, another adenoma prevention trial, PreSAP (Prevention of Spontaneous Adenomatopus Polyps) showed no increase in risk with celecoxib compared with placebo.[4] Based on the findings of the APC study, the administration of celecoxib in both trials was suspended, but celecoxib has not been withdrawn from the market in any country to date.

In response to these safety concerns with COX-2 inhibitors, regulatory authorities in several countries have conducted reviews of the available data. The Australian Drug Evaluation Committee (ADEC), the New Zealand Medicines Adverse Reactions Committee (MARC), the European Committee for Medicinal Products for Human Use (CHMP) and an advisory panel to the US FDA have all recently recommended restrictions of use and safety warnings regarding the risk of thrombotic cardiovascular events with COX-2 inhibitors.[5]

In New Zealand, the Intensive Medicines Monitoring Programme (IMMP) – a government funded proactive surveillance unit – has studied a cohort of approximately 60 000 patients who were prescribed rofecoxib or celecoxib. By the time rofecoxib was withdrawn, follow-up of about one-fifth of these patients had been completed. We consider that an interim analysis of the information collected by the IMMP is justified at this time. In many countries celecoxib is the most popular alternative to rofecoxib and it is now important to know if it carries the same cardiovascular risks as rofecoxib, which has been withdrawn from the market for this reason.

Methods

The IMMP undertakes prospective observational cohort studies on selected medicines in the postmarketing period and its methodology has previously been described in detail.[6] Essentially the IMMP performs prescription event monitoring (PEM) studies, in which cohorts of patients are established from prescription data. Clinical events during the use of the medicine are then identified from follow-up questionnaires to doctors and other sources.

The aim of this study was to compare the incidence of thrombotic cardiovascular events in patients taking celecoxib with the incidence in those taking rofecoxib, using the latter as the reference medicine cohort.

Study Cohorts

Monitoring of rofecoxib and celecoxib was conducted in parallel and began in December 2000, shortly after these medicines became available in New Zealand. Celecoxib was first marketed in late 1999 and rofecoxib was first marketed in early 2000. Prescription data for both medicines were entered for all patients who received a prescription between 1 December 2000 and 30 November 2001. The cohorts for this study were, therefore, defined as patients with at least one prescription for rofecoxib or celecoxib in this 1-year period.

Information entered into the IMMP cohort database for each medicine included patient details (name, address, national health identifier [NHI], date of birth and sex), prescription details (date of prescriptions, duration of each prescription, dose and whether use was 'as required' [prn] or continuous) and prescriber details.

1 The use of trade names is for product identification purposes only and does not imply endorsement.

© 2005 Adis Data Information BV. All rights reserved.

Identification of Thrombotic Cardiovascular Events

Thrombotic cardiovascular events were identified from several different sources: follow-up questionnaires, hospital admission data (from national databases), spontaneous reports and prescription data.

Follow-up questionnaires were sent out to each patient's doctor (usually the general practitioner) for rofecoxib and celecoxib simultaneously, by geographical area of New Zealand. For this interim analysis, the cohorts were separated into three groups at different stages of follow-up. As of 30 September 2004, follow-up had been sought for all patients in the first group; follow-up for the second group was ongoing, with questionnaires still to be sent; and no follow-up questionnaires had been sent out for patients in the third group.

Analyses were performed to check that the follow-up for rofecoxib and celecoxib had been conducted in parallel, including calculation of the proportion of follow-ups sent out and returned for each medicine in each of the groups.

In addition to the follow-up procedure, further events were identified from duplicate prescriptions and from spontaneous reports sent by health professionals using the national 'yellow card' reporting scheme.[6] Only reports for patients taking rofecoxib or celecoxib in the period 1 December 2000 to 30 November 2001 were included in this study. Another method of identifying clinical events was by comparison of the NHI with national morbidity and mortality databases to identify hospital admissions and deaths. This check was made at the time of the first prescription entry and on receipt of follow-up questionnaires if an event had been reported.

For group 1, thrombotic cardiovascular events were identified from returned follow-up questionnaires and the additional sources described. For group 2, events were identified from those questionnaires returned and from the other sources. For group 3, only events identified from the additional sources could be used.

Duration of Follow-Up

For patients with thrombotic cardiovascular events the 'on study' time was the duration until the event. Events identified and assessed before 30 September 2004 (date of withdrawal of rofecoxib) were included in this study. For all other patients who had been followed up, the on study time was defined as the period to the date the last follow-up questionnaire was completed (if still on the medicine) or the date of stopping the medicine (as recorded by the doctor on the questionnaire). All remaining patients were considered on study until the date their final prescription had expired.

Assessment of Thrombotic Cardiovascular Events

The clinical events that are identified by the IMMP are examined by clinical assessors and coded using terms from the IMMP dictionary, which is based on WHO-ART (WHO Adverse Reaction Terminology).[6] For this analysis, all events in the system organ class 'circulatory' that suggested myocardial infarction or stroke were re-examined by two clinical assessors. In addition to myocardial infarction, terms that suggested myocardial ischaemia (e.g. angina, unstable angina, ischaemic heart disease and cardiac chest pain) were included. All events coded as stroke or transient ischaemic attack (TIA) were included, but any that suggested haemorrhagic stroke or intracranial haemorrhage were excluded. Fatal and non-fatal thrombotic cardiovascular events for rofecoxib and celecoxib were included in this analysis.

For this study, events that occurred whilst the patient was taking the medicine or within 1 month of last drug exposure were included and events occurring more than 1 month after last exposure were excluded.[7] If a patient had more than one of the selected events (e.g. unstable angina followed by a myocardial infarction) only the first event was included. Each case record was also examined for evidence of pre-existing cardiovascular disease.

Additional Information on Cardiovascular Risk Factors

In addition to the information from the prescription data (age, sex, dose etc.) information on other potential cardiovascular risk factors was also available. The routine IMMP follow-up questionnaires requested information about indication for use of

© 2005 Adis Data Information BV. All rights reserved.

COX-2 inhibitors. For patients in the first seven geographical areas to be followed up, a supplementary questionnaire was also sent to doctors. This subset was comprised mostly of patients in the completely followed-up group, but included some from the partially followed-up group. The supplementary questionnaire included questions about concomitant aspirin (acetylsalicylic acid) [or other NSAID] use and pre-existing cardiovascular disease.

Analyses

Cox's proportional hazards models were used to account for the differing durations of treatment. For patients with adverse events matching our criteria, duration of use was defined as the time from the first prescription of a COX-2 inhibitor to the time of the event. For those for whom a follow-up form was returned and who were still taking the drug, the duration of use was from the date of the first prescription to the date the follow-up form was completed. For the remaining patients, the duration of use was from the date of the first prescription to the date of the last prescription plus the number of days of the last prescription. When the number of days was not stated, it was calculated from the dose and the number of tablets that were prescribed.

Patients who changed medicines were included in both cohorts (if both treatments were prescribed during the cohort collection period). The duration of treatment for each medicine was calculated independently as described previously. Where a patient had more than one course of treatment with the same medicine during the study period, only the last course of treatment was used in the analysis.

Cox's proportional hazards models were then applied to the data, using the drug, age, sex and whether use was prn or continuous, as independent variables. Indication for use of rofecoxib or celecoxib, concomitant aspirin/NSAID use and pre-existing cardiovascular disease (available from the sub-set of patients described in the previous section) were also added as independent variables. Separate models were fitted for each of the follow-up groups and for the overall data with these models using the follow-up group as a stratification variable. All analyses were carried out in STATA V8. The proportional hazards assumption was tested by using Schoenfeld residuals.

Results

Total Cohorts

For the period 1 December 2000–30 November 2001, 32 446 patients received at least one prescription for celecoxib and 26 403 patients received a prescription for rofecoxib. The age and sex distribution for each medicine is shown in table I.

The celecoxib cohort was significantly ($p < 0.0001$) older (62.7 years of age, SD 15.7) than the rofecoxib cohort (58.4 years of age, SD 17.5). There was no evidence of a sex difference between the rofecoxib and celecoxib cohorts (Pearson $\chi^2 = 0.07$, $Pr = 0.79$).

For the whole population, 77% of the rofecoxib patients were regular (daily) users and 23% received at least one prn prescription. In the celecoxib cohort, 80% were regular users and 20% were using celecoxib as required. The patterns of prescribed use for both medicines are shown in table II.

There were significantly more short-term users (both prn and daily) in the rofecoxib cohort and significantly more long-term regular users in the celecoxib cohort (tested by a χ^2 test for the pattern of use).

Dose

Data on daily dose were available for patients prescribed rofecoxib or celecoxib for regular (daily) use (table III). For this analysis the daily dose at the time of the last prescription was used. For patients prescribed prn prescriptions it was not possible to calculate a daily dose and, therefore, these subjects were excluded from this analysis.

Table I. Age and sex distribution for each cohort

Parameter	Rofecoxib (n = 26 403)	Celecoxib (n = 32 446)
Female sex [no. (%)]	15 979 (60.5)	20 008 (61.7)
Male sex [no. (%)]	10 173 (38.5)	12 200 (37.6)
Unknown sex [no. (%)]	251 (1.0)	238 (0.7)
Median age (years)	59	64
Inter-quartile age range (years)	47–72	52–75

© 2005 Adis Data Information BV. All rights reserved.

Table II. Patterns of prescribed use for rofecoxib and celecoxib cohorts

Type of use[a]	Rofecoxib [no. (%)]	Celecoxib [no. (%)]
As required[b]		
Short-term (up to 14 days)	1789 (6.8)	958 (2.9)
Long-term (>14 days)	4364 (16.5)	5541 (17.1)
Regular daily[c]		
Short-term (up to 14 days)	7206 (27.3)	5185 (16.0)
Long-term (>14 days)	13 040 (49.4)	20 754 (64.0)

a Information on usage was not available for four patients taking rofecoxib and eight patients taking celecoxib.

b As required (prn) use was identified from the prescription data stating 'take as required'.

c Regular daily use was identified from the prescription stating 'take x tablets x times daily'.

Indications for Use

Information on indications for use was available for 6720 celecoxib patients and 5177 rofecoxib patients. Individual indications (as recorded on the follow-up questionnaires) were grouped according to the aetiology of each condition and the results are shown in table IV.

Table IV shows that more celecoxib patients were using this medicine for osteoarthritis than rofecoxib (30% vs 20%) and more rofecoxib patients were using this medicine for unspecified pain than celecoxib (42% vs 32%). For indications that might be associated with an increased risk of thrombotic cardiovascular problems (some types of inflammatory arthritis and patients with cancer pain) there was no difference between the two medicines.

Follow-Up Sub-Groups

In group 1, where all follow-up questionnaires had been sent ('follow-up complete' group), 6267 patients were prescribed celecoxib (19% total celecoxib cohort) and 4882 patients were prescribed rofecoxib (18% total rofecoxib cohort). The response rate for returning the follow-up questionnaires for this group was 61.5% for celecoxib and 63.4% for rofecoxib.

In group 2, where follow-up was incomplete, there were 14 610 celecoxib patients (45% total celecoxib cohort) and 11 587 rofecoxib patients (44% total rofecoxib cohort). In group 3, the 'no follow-up' group, there were 11 569 celecoxib patients (36% total celecoxib cohort) and 9934 rofecoxib patients (38% total rofecoxib cohort).

Thrombotic Cardiovascular Events

For the total celecoxib cohort, 86 patients with thrombotic cardiovascular events were identified (0.27% of cohort). Of the 86 events, 60 (70%) were myocardial ischaemia/infarction and 26 (30%) were a cerebral thrombotic event (22 strokes and 4 TIAs). Of the 60 patients who experienced myocardial ischaemia/infarction, 34 died from this event and of the 26 patients who had a stroke or TIA, 18 died. Fifty-seven (66%) of the 86 patients with these cardiovascular events had documented pre-existing cardiovascular disease.

For the total rofecoxib cohort, 58 patients with thrombotic cardiovascular events were identified (0.22% of cohort). Of these 58 events, 42 (72%) were myocardial ischaemia/infarction and 16 (28%) were a cerebral thrombotic event (11 strokes, 3 TIAs, 1 recurrent TIAs and 1 cerebral thrombosis). Of the 42 patients who experienced myocardial ischaemia/infarction, 24 died from that event and of the 16 patients who had a cerebral event, 8 died. Thirty-seven (64%) of the 58 patients with these cardiovascular events had documented pre-existing cardiovascular disease.

Table V summarises the number of thrombotic cardiovascular events in each of the three follow-up sub-groups.

Table III. Dose distribution for regular users of rofecoxib and celecoxib

Dose (mg)	No. of patients (%)
Rofecoxib (n = 20 246)	
12.5	4911 (24.3)
25	13 061 (64.5)
50	2233 (11.0)
Other[a]	41 (0.2)
Celecoxib (n = 25 949)	
100	1851 (7.1)
200	21 169 (81.6)
400	2821 (10.9)
Other[a]	108 (0.4)

a Other or unknown doses.

© 2005 Adis Data Information BV. All rights reserved.

Table IV. Indication for use of celecoxib or rofecoxib

Indication for use	Rofecoxib [no. (%)]	Celecoxib [no. (%)]
All	5177	6720
Injury	154 (3.0)	193 (2.9)
Inflammatory arthritis[a]	178 (3.4)	258 (3.8)
Osteoarthritis	1016 (19.6)	2044 (30.4)
Pain – musculoskeletal	1307 (25.2)	1831 (27.3)
Pain – unspecified	2175 (42.0)	2173 (32.3)
Pain – other[b]	339 (6.6)	210 (3.1)
Miscellaneous	8 (0.2)	11 (0.2)

a The term 'inflammatory arthritis' includes the individual conditions rheumatoid arthritis, ankylosing spondylitis, polymyalgia rheumatica and gout.

b Other pain included acute pain, nerve pain, gynaecological pain and cancer pain. The incidence of patients with cancer was 0.5% in each group (i.e. no difference).

Effect of Dose

Comparison of the rate of thrombotic cardiovascular events for the most commonly prescribed doses for each medicine (rofecoxib 12.5mg, 25mg and 50mg; celecoxib 100mg, 200mg and 400mg) showed no dose effect. However, the number of events in each dose stratification was very small, particularly for the higher doses, for example there were only two events for rofecoxib 50mg.

Time to Onset of Event

For the 86 celecoxib events and the 58 rofecoxib events (total 144 events), time to onset of event was known for 142 events (table VI). For patients taking celecoxib the median time to event was 83 days (inter-quartile range 27–330) and for rofecoxib was 57 days (inter-quartile range 21–204).

Rates of Cardiovascular Thrombotic Events

In the group in whom follow-up had been completed (group 1) the unadjusted hazard ratio for celecoxib compared with rofecoxib was 1.07 (95% CI 0.59, 1.93). After an adjustment for age, this hazard ratio was 0.94 (95% CI 0.51, 1.70). A further adjustment for sex, prn use, indication for use, concomitant aspirin/NSAID use and pre-existing cardiovascular disease resulted in only minor changes.

In the partially followed-up group, the age-adjusted hazard ratio for celecoxib compared with rofecoxib was 0.60 (95% CI 0.38, 0.95) and in the group who had not been followed up, the hazard ratio was 0.40 (95% CI 0.13, 1.22). Cox's proportional hazards regression models for the three groups combined violated the proportional hazards assumption, so results for the total cohorts are not presented.

Discussion

This interim analysis of our postmarketing study of celecoxib and rofecoxib indicates that in a group of approximately 11 000 patients who had been followed up by 30 September 2004, there was no significant difference in the risk of thrombotic cardiovascular events with celecoxib compared with rofecoxib, although the confidence intervals were wide.

The IMMP cohorts were split into three groups for analysis because follow-up of all of the patients had not been completed. Although this was necessary in order to apply the most appropriate statistical methods, it limited the power to detect differences between celecoxib and rofecoxib in the three subgroups. The most confidence can be placed in the results from the group who had been completely followed up using the routine IMMP methodology. One strength of this active surveillance is that adverse events are identified from multiple sources, including questionnaires to doctors, prescription data, spontaneous reports and information from national databases. The results from the groups in whom follow-up had not been completed are less reliable because events had (largely) been identified from sources other than the follow-up questionnaires. These sources, especially spontaneous reporting, may be subject to reporting bias, for example doctors may have reported more cardiovascular events with rofecoxib following the publication of

Table V. Thrombotic cardiovascular events by follow-up group

Group	Rofecoxib		Celecoxib	
	No. of patients	Events	No. of patients	Events
Follow-up complete	4882	16	6267	37
Follow-up incomplete	11 587	35	14 610	43
Not followed up	9934	7	11 569	6
Total	**26 403**	**58**	**32 446**	**86**

© 2005 Adis Data Information BV. All rights reserved.

Table VI. Time to onset of thrombotic cardiovascular events in patients taking celecoxib compared with patients taking rofecoxib

Time to onset of event	Rofecoxib [no. (%)]	Celecoxib [no. (%)]
≤7 days	4 (7)	4 (5)
8–30 days	14 (24)	22 (26)
31–60 days	12 (21)	12 (14)
61–90 days	5 (9)	6 (7)
91–180 days	8 (14)	9 (11)
181–360 days	7 (12)	15 (18)
>360 days	8 (14)	16 (19)

the VIGOR (Vioxx® Gastrointestinal Outcomes Research) trial in May 2000.[8]

It was considered acceptable to perform this comparison of the IMMP celecoxib cohort with the rofecoxib cohort because the monitoring of these two COX-2 inhibitors had been conducted in parallel. However, it was important to evaluate any potential differences between the two cohorts that might confound the results of this observational study. The celecoxib cohort was older and more patients were taking the medicine long-term. A higher proportion of celecoxib users were taking a concomitant NSAID and had pre-existing cardiovascular disease. We accounted for these differences by adding several variables to the statistical models, but after adjustment for age, adjustment for other variables made little difference to the results. The IMMP does not routinely collect information on other potential confounding variables for cardiovascular disease (e.g. smoking or obesity), but there is some evidence that patients taking celecoxib or rofecoxib do not differ in this respect.[9]

Data on dose were available for almost all patients and although we have presented these results, dose was not included as a variable in the statistical models for the hazard ratios. It was considered that in this comparative study, estimating dose equivalence between rofecoxib and celecoxib (in order to adjust the results) could be misleading. We attempted to study dose relationship with cardiovascular events for each individual medicine, but as the number of events in the higher dose levels was very small, the result of no evident dose effect must be interpreted with caution.

In 2004, a comprehensive review concluded that "the pharmacological evidence together with concerns arising from some clinical studies suggests that an increased cardiovascular risk associated with COX-2 inhibitor use remains a possibility".[10] Further studies of the cardiovascular effects of COX-2 inhibitors have now been published. Two placebo-controlled trials of rofecoxib and celecoxib (designed to show efficacy in the prevention of colonic polyps) have shown that both medicines increase thrombotic cardiovascular events, which suggests a class effect.[11] However, several observational studies in large populations taking NSAIDs or COX-2 inhibitors have suggested an increased cardiovascular risk for rofecoxib, but not for celecoxib.[9,12,13] Two recent case-control studies have also suggested a lower risk of myocardial infarction with celecoxib compared with rofecoxib.[14,15]

However, there have not been any direct comparative (head-to-head) clinical trials of celecoxib versus rofecoxib.[16] Such a trial is unlikely to be performed, thus increasing the importance of observational studies of the type performed by the IMMP. Although there are limitations of observational studies, there are some advantages of postmarketing studies over clinical trials. PEM studies examine how medicines are used in 'real life', with no exclusion criteria and generally in larger populations for longer periods of time than clinical trials.

Conclusion

Our results from the analysis of approximately 11 000 patients in the IMMP cohorts, suggest there is no significant difference in cardiovascular risk for patients taking celecoxib compared with those taking rofecoxib. However, the number of events in the followed-up sub-group was small and the confidence intervals for the hazard ratio were wide. Follow-up of the remaining patients would provide more insight into the results presented in this interim analysis.

Acknowledgements

Funding statement: the IMMP receives the majority of its funding from the New Zealand Ministry of Health and the work presented in this report has largely been funded by this source. General donations towards the work of the IMMP are also received from some pharmaceutical companies. However, these donations are unconditional and the companies have no role in the analysis or interpretation of IMMP data and are not involved in the decision to publish results.

© 2005 Adis Data Information BV. All rights reserved.

Conflict of interests statement: the authors declare that they have no competing interests that might affect this report.

We would like to acknowledge David Coulter, who as former Director of the IMMP initiated the IMMP monitoring of the cyclo-oxygenase (COX)-2 inhibitors and performed all of the initial clinical coding of events for this study. The data processors of the IMMP contributed a huge effort in entering all of the data analysed in this report. We thank them for their commitment to the programme, especially during a time when its future was under threat. We also thank Ruth Savage for her help and rheumatology expertise in assessing the indications for use of COX-2 inhibitors and David Clark for his advice. In addition, we are most grateful to Lianne Parkin and Charlotte Paul for their advice regarding design for this study and for reviewing the manuscript.

References

1. Singh D. Merck withdraws arthritis drug worldwide. BMJ 2004; 329: 816
2. Bresalier RS, Sandler RS, Quan H, et al. Cardiovascular events associated with rofecoxib in a colorectal adenoma chemoprevention trial. N Engl J Med 2005; 352: 1092-102
3. Solomon SD, McMurray JJV, Pfeffer MA, et al. Cardiovascular risk associated with celecoxib in a clinical trial for colorectal adenoma prevention. N Engl J Med 2005; 352: 1071-80
4. Ketelbey B (Pfizer NZ Ltd). Letter to New Zealand doctors. 2004 Dec 23
5. World Health Organisation. Information exchange system: cyclooxygenase-2 (COX-2) inhibitor medicines. 2005 Feb 28. QSM/MC/IEA.111
6. Coulter DM. The New Zealand intensive medicines monitoring programme in pro-active safety surveillance. Pharmacoepidemiol Drug Saf 2000; 9: 273-80
7. White WB, Faich G, Borer JS, et al. Cardiovascular thrombotic events in arthritis trials of the cyclo-oxygenase-2 inhibitor celecoxib. Am J Cardiol 2003; 92: 411-8
8. Bombardier C, Laine L, Reicin A, et al. Comparison of upper gastrointestinal toxicity of rofecoxib and naproxen in patients with rheumatoid arthritis. N Engl J Med 2000; 343: 1520-8
9. Solomon DH, Schneeweiss S, Glynn RJ, et al. Relationship between selective cyclooxygenase-2 inhibitors and acute myocardial infarction in older adults. Circulation 2004; 109: 2068-73
10. Clark DWJ, Layton D, Shakir SAW. Do some inhibitors of COX-2 increase the risk of thromboembolic events? Linking pharmacology with pharmacoepidemiology. Drug Saf 2004; 27 (7): 427-56
11. Drazen JM. COX II inhibitors: a lesson in unexpected problems [online]. Available from URL: http://www.nejm.org [Accessed 2005 Feb 15]
12. Ray WA, Stein CM, Hall K, et al. Non-steroidal anti-inflammatory drugs and risk of serious coronary heart disease: an observational cohort study. Lancet 2002; 359: 118-23
13. Mamdani M, Rochon P, Juurlink DN, et al. Effect of selective cyclo-oxygenase-2 inhibitors and naproxen on the short term risk of acute myocardial infarction in the elderly. Arch Intern Med 2003; 163 (4): 481-6
14. Kimmel SE, Berlin JA, Reilly M, et al. Patients exposed to rofecoxib and celecoxib have different odds of nonfatal myocardial infarction. Ann Intern Med 2005; 142: 157-64
15. Graham DJ, Campen D, Hui R, et al. Risk of acute myocardial infarction and sudden cardiac death in patients treated with cyclo-oxygenase 2 selective and non-selective non-steroidal anti-inflammatory drugs: nested case-control study [online]. Available from URL: http://image.thelancet.com [Accessed 2005 Jan 25]
16. Topol EJ. Arthritis medicines and cardiovascular events: "house of coxibs". JAMA 2005; 293 (3): 366-8

Correspondence and offprints: Dr *Mira Harrison-Woolrych*, Intensive Medicines Monitoring Programme, Department of Preventive and Social Medicine, University of Otago, Box 913, Dunedin, New Zealand.
E-mail: mira.harrison-woolrych@stonebow.otago.ac.nz

© 2005 Adis Data Information BV. All rights reserved.