SHORT COMMUNICATION

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NSAID Use in Individuals at Risk of Renal Adverse Events

An Observational Study to Investigate Trends in Australian Veterans

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Abstract

Background: Cyclo-oxygenase (COX)-2 inhibitors were introduced to world markets with claims of improved gastrointestinal safety compared with traditional NSAIDs. Randomized clinical trials had demonstrated fewer adverse gastrointestinal events with COX-2 inhibitors, but no difference with other adverse events, including adverse renal events. There was a rapid uptake of these medicines.

Objective: To compare uptake rates of NSAIDs, including COX-2 inhibitors, in a reference population with those in two high-risk populations: a population taking medicines affecting the renin-angiotensin system and loop diuretics, and a population taking medicines for diabetes mellitus.

Method: An observational study was undertaken in which the Department of Veterans' Affairs claims dataset was used to identify: veterans dispensed ACE inhibitors (ACEIs) or angiotensin II type 1 receptor antagonists (angiotensin receptor blockers [ARBs]) and furosemide (ACEI-ARB/furosemide cohort); veterans dispensed medicines for diabetes (diabetes cohort); and all other veterans (reference cohort) from July 1999 to July 2007. Concurrent dispensing of NSAIDs was assessed.

Results: Prior to celecoxib becoming subsidized in Australia, the baseline level of NSAID use was 19.5% in the reference cohort, 15.3% in the diabetes cohort and 15.6% in the ACEI-ARB/furosemide cohort. After the listing of celecoxib, utilization of NSAIDs increased by 42.2% in the reference cohort, with similar increases in the diabetes cohort (40.8%; $p = 0.88$ compared with the reference cohort) and the ACEI-ARB/furosemide cohort (49.6%; $p = 0.09$ compared with the reference cohort). With the withdrawal of rofecoxib, utilization of NSAIDs in the reference cohort fell by 25.3%, with similar falls in the diabetes cohort (24%; $p = 0.28$ compared with the reference cohort) and the ACEI-ARB/furosemide cohort (26.1%; $p = 0.43$ compared with the reference cohort).

Conclusions: Despite the increased vulnerability of veterans receiving ACEI-ARB/furosemide or diabetes medicines to adverse events of NSAIDs, uptake rates of COX inhibitors were equivalent to the rest of the veteran population. This suggests the gastrointestinal safety messages were interpreted broadly by prescribers and the adverse renal effects were not considered.

Background

Adverse drug events are very common, with an earlier Australian study suggesting that 10.6% of the population had experienced an adverse drug event in the previous 6 months.[1] Studying utilization of medicines in populations vulnerable to adverse drug events is particularly important if we are to develop ways of minimizing adverse drug events. Because celecoxib and rofecoxib were marketed as having a safer gastrointestinal adverse effect profile compared with traditional NSAIDs, but did not have a safer renal adverse effect profile,[2,3] we investigated patterns of NSAID use in populations at risk of adverse effects from these medicines. This provided an opportunity to understand use and discontinuation patterns in vulnerable groups.

The cyclo-oxygenase (COX)-2 inhibitors were introduced to the Australian market in 1999 and subsidized under the Pharmaceutical Benefits Scheme (PBS) in August 2000. As has been reported,[4] a rapid uptake of these medicines followed. At the time of the introduction to the market, celecoxib and rofecoxib were associated with claims of an improved gastrointestinal safety profile;[2,3] however, this has been the subject of debate.[5] While short-term studies of <12 weeks suggested these medicines had a lower incidence of adverse gastrointestinal events,[6] the long-term trials were more equivocal.[2,3] The US FDA review of celecoxib reported no significant difference in the incidence of clinically significant upper gastrointestinal events with the comparator NSAIDs.[3] The VIGOR (Vioxx Gastrointestinal Outcomes Research) trial of rofecoxib found a reduction in adverse gastrointestinal events but an increase in adverse cardiovascular events compared with naproxen.[2] In addition to their adverse gastrointestinal profile, NSAIDs have also been associated with adverse renal effects. The FDA review of celecoxib found that similar renal effects were observed with celecoxib compared with ibuprofen and diclofenac.[3] The review of rofecoxib found a greater rate of discontinuations for rofecoxib in comparison with naproxen for hypertension-related events (rate ratio [RR] 4.67; $p < 0.001$), with trends towards higher discontinuations for oedema-related events (RR 1.92; $p = 0.057$) and heart failure-related events (RR 2.11; $p = 0.065$), with no difference in renal-related discontinuations (RR 1.14; $p = 0.8$).[7]

The population at risk of adverse renal effects from NSAIDs was well described prior to the launch of COX-2 inhibitors. The 'triple whammy' is an adverse effect resulting from the combination of medicines acting on the renin-angiotensin system, diuretics and NSAIDs. This acts through prostaglandin-mediated effects of the NSAID and angiotensin effects of the ACE inhibitor (ACEI)/angiotensin II type 1 receptor antagonist (angiotensin receptor blocker [ARB]) on renal function, in conjunction with the diuretic effects on renal volume, which puts people at risk of renal dysfunction.[8] People with heart failure are also known to be vulnerable to the adverse effects of NSAIDs.[9] Older people with diabetes mellitus also appear to be more vulnerable to the renal effects of NSAIDs, as are those with hypertension.[10]

The aim of this study was to compare uptake rates of NSAIDs in a reference population with that in a population taking medicines for diabetes and in a population taking medicines affecting the renin angiotensin system (ACEIs or ARBs) and loop diuretics, of which furosemide was the example, prescribed in the population studied in this investigation. The rapid uptake of COX-2 inhibitors in Australia[4] provided the opportunity to determine whether a more cautious uptake occurred in the population at risk of renal adverse events. The population taking medicines affecting the renin-angiotensin system together with furosemide was chosen, as this group is vulnerable to the 'triple whammy' effect.[8] It is also likely to reflect the population with heart failure.[11] The population with diabetes may also be considered vulnerable as this group is at high risk of cardiovascular and renal complications associated with their disease.[12]

Research Design and Methods

The Department of Veterans' Affairs (DVA) Pharmacy Claims Database contains details of all prescription medicines dispensed to veterans for which DVA pay a subsidy. The data file contains 75 million records for a treatment population of 310 000 veterans. The DVA maintains a client file, which includes data on sex, date of birth, date of death and family status. Medicines are coded in the

dataset according to the WHO anatomical and therapeutic chemical (ATC) classification.[13]

Three groups of veterans were selected:

1. Group 1 (reference cohort): veterans dispensed at least one prescription, but not dispensed medicines used for treatment of diabetes, ACEI, ARB or furosemide.
2. Group 2 (diabetes cohort): veterans dispensed medicines for diabetes.
3. Group 3 (ACEI-ARB/furosemide cohort): veterans dispensed an ACEI or ARB and furosemide.

For each group the prevalent population was defined each month from July 1999 to July 2007. Group 1 included all veterans who had had a dispensing in that month, but were not included in groups 2 or 3. For group 2, in each month patients were deemed to be taking medicines for diabetes if they had had a dispensing of an oral hypoglycaemic within the previous 35 days or insulin within the last 122 days. These time intervals were calculated from the data and represent the number of days within which 75% of the population have a repeat prescription dispensed, thus most likely to represent periods of actual consumption. Oral hypoglycaemics and insulins included all those in the ATC classification A10.[13] Group 3 included veterans who were dispensed an ACEI or ARB in the previous 39 days and furosemide in the previous 107 days. ACEIs and ARBs included all those in the ATC classification C09.[13]

Having defined the prevalent populations, the proportion concurrently dispensed NSAIDs was calculated as those with an oral NSAID dispensing in the previous 49 days. NSAIDs included all those in the ATC classification M01A.[13]

Interrupted time series and segmented regression have been used to estimate the change in level and trend of series for pharmaceuticals;[14] however, these models fail to take into account the variability in the data that arises from calculating the point estimate within a month. To overcome this, we fitted a log-binomial generalized estimating equation, to allow for clustering of patients with an independent error structure at the patient level. All analyses were undertaken using SAS v9.1. (SAS Institute Inc., Cary, NC, USA).

For each cohort we assumed that three distinct linear relationships existed over time, with two breakpoints: the first at 1 September 2000 and the second at 1 March 2005. Consistent with recommended methods,[14] the period of January 2000 to August 2000 was excluded from the analysis because anecdotal evidence suggested that samples were available that were not captured in the administrative data and may have led to the observed decline immediately prior to PBS listing. If this period had not been excluded, an overestimate in uptake might have occurred. Five months of data were also excluded after October 2004 to account for the lag in effect of the withdrawal of rofecoxib.

Ethics approval for this study was obtained from the DVA Ethics Committee and the Human Research Ethics Committee of the University of South Australia.

Results

Table I provides details of the numbers in each cohort, their age and sex at the start of the study. Figure 1 provides the trends in utilization of NSAIDs for each of the three groups of veterans. Prior to the listing of celecoxib on the PBS/Repatriation Pharmaceutical Benefits Scheme (RPBS) in August 2000, the baseline level of NSAID use in the reference cohort was 19.5%; for the diabetes cohort it was 15.3% and in the ACEI-ARB/furosemide cohort it was 15.6% (table II). Baseline use in the reference cohort was higher than the other two cohorts ($p < 0.0001$) [table II].

The listing of celecoxib on the PBS/RPBS in August 2000 led to a marked increase in utilization of NSAIDs in all three groups. The proportion of veterans taking NSAIDs increased in the reference cohort by 42.2%, in the diabetes cohort by 40.8% and in the ACEI-ARB/furosemide cohort by 49.6% (table II). The proportional increase was similar in

Table I. Number, age and sex of subjects in each cohort at study start

Age/sex	Reference cohort (n = 185 705)	Diabetes mellitus cohort (n = 16 016)	ACEI-ARB/ furosemide cohort (n = 15 386)
Average age, y (SD)	75.2 (9.1)	75.6 (7.5)	75.6 (7.5)
Male sex (%)	65	71	65

ACEI = ACE inhibitor; **ARB** = angiotensin receptor blocker; **SD** = standard deviation.

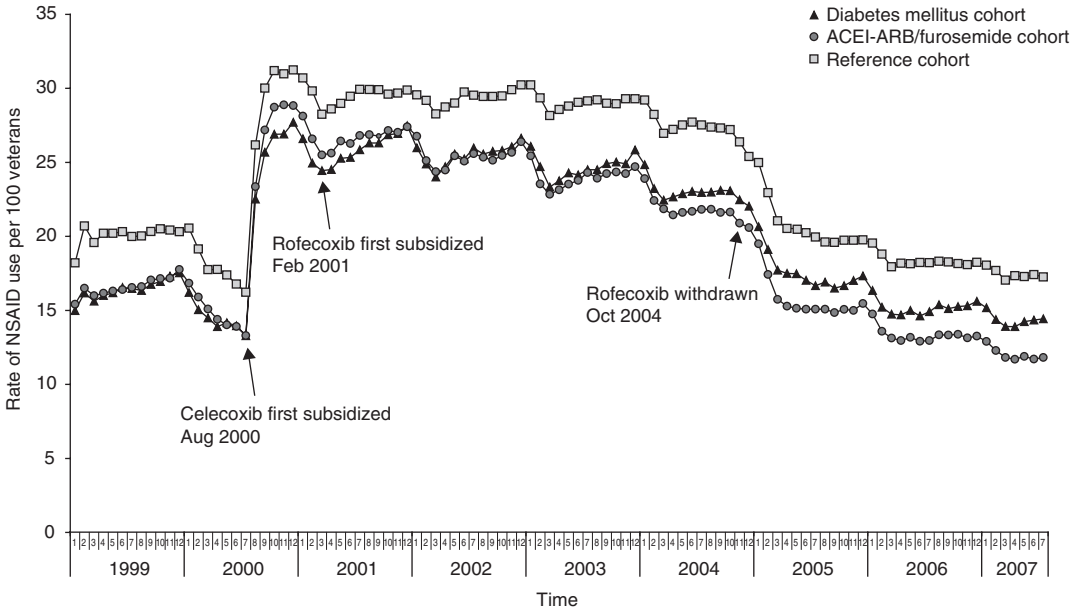

Fig. 1. Rate of veterans dispensed NSAIDs; 1999 to July 2007. **ACEI** = ACE inhibitor; **ARB** = angiotensin receptor blocker.

the diabetes cohort (p = 0.88) and the ACEI-ARB/furosemide cohort (p = 0.09) compared with the reference cohort (table III).

In the 50 months after which celecoxib entered the market and before rofecoxib was withdrawn, there was a decline in the use of NSAIDs in the reference cohort of 0.2% per month (table II). A decline was also observed in the diabetes cohort of 0.3% per month and in the ACEI-ARB/furosemide cohort of 0.5% per month (table II). The rate of decline during this time was similar in the diabetes and reference cohort (p = 0.22). However, a significantly greater decline was observed in the ACEI-ARB/furosemide cohort than in the reference cohort (p < 0.0001) [table III].

With the withdrawal of rofecoxib the proportion of veterans receiving NSAIDs in the reference cohort fell by 25.3%, while in the diabetes cohort it fell by 24% and in the ACEI-ARB/furosemide cohort it decreased by 26.1% (table II). The withdrawal of rofecoxib saw a similar fall in both the diabetes cohort (p = 0.28) and the ACEI-ARB/furosemide

Table II. Within-group differences for trends and level of utilization for NSAID use in the three cohorts

Parameter	Reference RR (95% CI)[a]	Diabetes mellitus RR (95% CI)[a]	ACEI-ARB/furosemide RR (95% CI)[a]
Baseline level of utilization of NSAIDs	0.195 (0.193, 0.197)	0.153 (0.147, 0.158)	0.156 (0.150, 0.162)
Baseline trend in utilization of NSAIDS	1.005 (1.004, 1.006)	1.011 (1.007, 1.015)	1.010 (1.006, 1.014)
Change in level of utilization after celecoxib came on to the market	1.422 (1.404, 1.441)	1.408 (1.337, 1.482)	1.496 (1.414, 1.582)
Change in trend of utilization after celecoxib came on to the market	0.998 (0.998, 0.998)	0.997 (0.997, 0.998)	0.995 (0.994, 0.995)
Change in level of utilization after withdrawal of rofecoxib	0.747 (0.742, 0.752)	0.760 (0.742, 0.779)	0.739 (0.720, 0.759)
Change in trend of utilization after withdrawal of rofecoxib	0.992 (0.992, 0.993)	0.991 (0.989, 0.992)	0.988 (0.987, 0.990)

a All p-values were <0.0001.

ACEI = ACE inhibitor; **ARB** = angiotensin receptor blocker; **RR** = rate ratio.

Table III. Comparison of NSAID use and changes in NSAID use over time between the three cohorts

Utilization	Diabetes mellitus vs reference cohort RR (95% CI)	p-Value	ACEI-ARB/furosemide vs reference cohort RR (95% CI)	p-Value
Baseline trend in NSAID utilization	1.005 (1.001, 1.009)	0.011	1.005 (1.001, 1.009)	0.019
Change in level of utilization of NSAIDs after celecoxib came on to the market	0.995 (0.939, 1.055)	0.88	1.051 (0.992, 1.114)	0.090
Change in trend of NSAID utilization after celecoxib came on to the market	1.0 (0.999, 1.00)	0.216	0.997 (0.996, 0.997)	<0.0001
Change in level of utilization of NSAIDs after withdrawal of rofecoxib	1.015 (0.988, 1.043)	0.28	0.989 (0.962, 1.017)	0.43
Change in trend of utilization of NSAIDs after withdrawal of rofecoxib	0.999 (0.998, 1.001)	0.31	0.996 (0.994, 0.998)	<0.0001

ACEI = ACE inhibitor; **ARB** = angiotensin receptor blocker; **RR** = rate ratio.

cohort (p = 0.43) compared with the reference cohort (table III).

Over the entire study, the proportion of COX-2 inhibitor usage amongst total NSAID use was similar in the three cohorts (figure 2).

Discussion

This study examined NSAID utilization in two groups at higher risk of renal adverse events, those taking medicines for diabetes and those receiving ACEIs or ARBs with the loop diuretic furosemide, compared with a reference cohort. The uptake of NSAIDs at the time of the launch of COX-2 inhibitors in the diabetes cohort and in the ACEI/furosemide cohort was equivalent to the uptake in the reference cohort. After the initial uptake, usage of NSAIDs reduced at a similar rate in the diabetes and reference cohorts, and at a slightly faster rate in the ACEI-ARB/furosemide cohort compared with the reference cohort, until the withdrawal of rofecoxib from the market in October 2004. The withdrawal led to a drop in NSAID use in all three groups, similar to levels prior to COX-2 inhibitors entering the market.

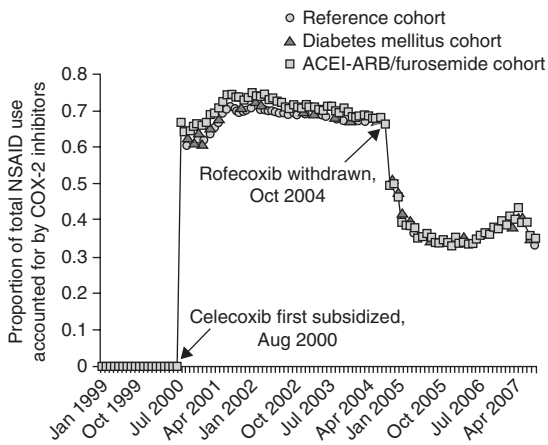

Fig. 2. Proportion of NSAID use in each cohort accounted for by cyclo-oxygenase (COX)-2 inhibitors. **ACEI** = ACE inhibitor; **ARB** = angiotensin receptor blocker.

These findings raise some important questions about the presentation of safety data for general practitioners and consumers and the promotion of safe use of medicines in vulnerable populations. The COX-2 inhibitors were marketed with claims of improved gastrointestinal safety. We are not aware of any claims of superior renal safety; however, our results raise questions as to whether the superior gastrointestinal safety claims were interpreted as greater safety generally, given that uptake rates in the high-risk groups were equivalent to or higher than those in the general population, not lower as might be anticipated if risk was appropriately assessed. This is speculative and qualitative research would need to be undertaken to clarify this issue. Such research is imperative because, from a quality use of medicines perspective, it is essential to present safety data accurately to help ensure that appropriate selection of therapy is made. This will contribute to safe and effective use of medicines.

The other issues that this research highlights are the importance of post-marketing surveillance studies and the timely feedback of results to practitioners. The time between the listing of celecoxib and the withdrawal of rofecoxib was 50 months. The high rate of NSAID use in these vulnerable populations was observed throughout this entire period. Post-marketing surveillance with timely feedback to

practitioners may have resulted in an earlier reduction in use amongst the vulnerable population. The USA Institute of Medicine's future of drug safety report highlights the need for greater funding and staffing for drug safety monitoring activities and the need for regulatory authority and delineation of roles in communicating risk benefit information of marketed products.[15]

The main limitation of this study is the lack of outcome data. However, case-control studies have demonstrated that those with heart failure have an increased risk of hospitalization due to concurrent NSAID use.[16] NSAID use in patients with heart failure, hypertension or diabetes has also been demonstrated to be associated with a higher risk of acute renal failure.[10] The Australian Adverse Drug Reactions Advisory Committee (ADRAC) published an article in June 2000 highlighting nine reports of renal failure associated with celecoxib, with six in patients taking an ACEI and diuretic concurrently.[17] The ADRAC again highlighted the issue in August 2003 stating that "ACE inhibitors, NSAIDs and diuretics, individually or in combination, are involved in over 50% of cases of iatrogenic acute renal failure reported to ADRAC."[18] Twenty-eight of the 129 reports to the ADRAC of acute renal failure involved an NSAID prescribed with an ACEI or an ARB and furosemide: the fatality rate of cases involving this 'triple whammy' was 10%.[18] Given these results, and the increased rates of use in high-risk populations in Australia, it is likely that an increased number of veterans experienced adverse reactions associated with NSAID use.

The veteran population have slightly more general practice visits (RR 1.17; $p < 0.05$) and hospitalizations (RR 1.21; $p < 0.05$) per year than other Australians aged 40 years and over, but veterans with no service-related disability have levels similar to those of other Australians.[19] Similar numbers of prescriptions per general practitioner visit are observed between the veteran population and the Australian population as a whole. However, because of the higher rate of general practitioner visits, veterans receive slightly more prescriptions annually than other Australians (RR 1.13; $p < 0.05$).[19] This suggests that our study results are likely to be similar to those occurring in the Australian population generally, but may slightly over-estimate the effect.

Conclusion

This study demonstrates equivalent uptake of NSAIDs in patients at high risk of adverse effects compared with the general population. The results suggest more attention needs to be paid to the delivery of medicine safety information, particularly that highlighting the need for caution in vulnerable groups.

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