A Population Based Historical Cohort Study of the Mortality Associated with Nabumetone, Arthrotec®, Diclofenac, and Naproxen

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ABSTRACT. Objective. To identify the unbiased differences in all cause mortality among populations using 4 non-steroidal antiinflammatory drugs (NSAID): nabumetone, Arthrotec, diclofenac plus a cytoprotective agent dispensed separately (diclofenac+), and naproxen.

Methods. We performed a population based historical cohort study using linked data from several provincial health care databases. Logistic regression was used to produce estimates of the mortality associated with the study drugs unbiased by known confounders. The entire population of the province of Saskatchewan, Canada entitled to drug plan benefits in 1995 was eligible (approximately 91% of 1 million people). Participants were identified if they filled a prescription for one of the 4 study NSAID (18,424 individuals). They were then followed forward in time for 6 months to determine all cause mortality.

Results. Compared to nabumetone, the adjusted odds of death for participants taking Arthrotec was 1.4 (95% confidence interval, CI: 0.9-2.1), for diclofenac+ 2.0 (1.3-3.1), and naproxen 3.0 (1.9-4.6).

Conclusion. The multivariate analysis showed patients taking nabumetone and Arthrotec had significantly lower mortality than those taking other study drugs. Nabumetone had 1/3 to 1/5 the mortality associated with the diclofenac+ and naproxen groups. It appears that inherent gastroprotective strategies in the study NSAID may translate into decreased mortality at the population level. (J Rheumatol 2004;31:951–6)

Key Indexing Terms:

NSAID MORTALITY RELATIVE RISK NAPROXEN
NABUMETONE ARTHROTEC DICLOFENAC

Today nonsteroidal antiinflammatory drugs (NSAID) are one of the most commonly prescribed classes of drugs in the world[1]. Over 300,000 prescriptions were dispensed in Saskatchewan alone in 1995 to 14% of the total eligible population (from written data provided to authors from Saskatchewan Health). In the USA, prescriptions for NSAID represent 4.5% of all prescriptions written[2], not accounting for the widespread use of aspirin and other NSAID available over the counter.

Many different brands and sub-types of NSAID are available, each of which has its own particular claimed efficacy and side effect profile. However, significant adverse effects associated with the use of these drugs have been reported. Potentially life threatening hepatotoxicity[3-5], renal dysfunction[6,7], heart failure[8], angioedema[9], bronchospasm[10], and hematological disturbances[11] are all well recognized complications of NSAID therapy. By far the most common problem is gastrointestinal (GI) side effects[12-17]. These can range from dyspepsia (heartburn) through to peptic ulceration, hemorrhage, and death. Adverse events are magnified by the over-representation of the elderly as users of the drug class. Older age is particularly associated with more frequent and worse side effects[18-20]. In some reports, the proportion of NSAID users over 65 years is as high as 90%[21], while in the province of Saskatchewan, Canada, in 1995, this figure was approximately 55% (from written data provided to authors from Saskatchewan Health).

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Supported by an unrestricted grant from Searle Canada and Searle USA to Dr. Peloso.

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Submitted July 2, 2003; revision accepted December 3, 2003.

A number of pharmacological efforts have been made over the past decade or so to reduce NSAID side effects, including enteric coating tablets, parenteral administration, and formulation of pro-drugs designed to bypass absorption in the upper gastrointestinal tract. More recent efforts have focused on the concurrent use of a gastroprotective agent with the NSAID (such as misoprostol or ranitidine). Arthrotec® was released in the early 1990s and is a combination tablet of an older NSAID (diclofenac) and misoprostol. Misoprostol has been shown in large randomized trials to reduce the rate of perforations, ulcers, and bleeds[22]. Most recent, newly developed NSAID have selectively blocked the activity of the cyclooxygenase (COX) enzymes. It appears that the COX-2 enzyme principally mediates the antiinflammatory effects and the COX-1 enzyme is responsible for the gastroduodenal damaging effects. Existing older NSAID block the activity of both COX-I and COX-II and therefore, although they are effective antiinflammatory agents, they also cause gastrointestinal damage. A drug that selectively blocks the activity of COX-II will theoretically produce an antiinflammatory effect without gastrointestinal side effects.

Nabumetone (Relafen®) is a newer NSAID that was listed in the Saskatchewan Formulary with unrestricted coverage in January 1995. It is a non-acidic pro-drug that may also have some intermediate COX-II selectivity. More recently COX-II specific NSAID have been marketed such as celecoxib and rofecoxib, that have greater selectivity/specificity for the COX-II enzyme.

Some of these approaches have established their efficacy in reducing gastrointestinal morbidity through randomized trials[22-24], but their actual effectiveness in reducing mortality in the general population of NSAID users is far from clear.

Using data from the Arthritis, Rheumatism, and Aging Medical Information System (ARAMIS)[25] Fries, *et al*[26] found an excess mortality rate (from gastrointestinal causes alone) of 0.18% per year for those taking NSAID. Almost a decade later the figure is 0.22% per year[27], with NSAID users being 4.21 times more likely to die than non-users. This rate translates into approximately 16,500 excess deaths per year in the USA alone due to the widespread use of these drugs (more than all deaths attributable to cervical cancer, malignant melanoma, and asthma combined[15]). This figure fits well with the Food and Drug Administration post-marketing surveillance findings of 10–20,000 excess NSAID related deaths/year[29]. Elderly patients appear to be of particular increased risk of NSAID side effects[30,31].

The evidence for NSAID-associated mortality in the World literature is surprisingly limited. We undertook this population-based historical cohort study to see if there was a difference in mortality rates in patients taking 4 different NSAID or NSAID/drug combinations. At the time of the study (1995) nabumetone and Arthrotec were the "newest" NSAID on the Saskatchewan formulary whereas naproxen and diclofenac had been in use for many years. The study was therefore initially designed as a comparison of mortality between "newer" and "older" NSAID.

MATERIALS AND METHODS

Design. This was a historical cohort study using linked data from 4 Saskatchewan health-services databases. A cohort was formed of all individuals who filled a prescription for one of the 4 study NSAID in the calendar year 1995. The databases were then used to capture health-related services for 4 years prior (comorbidity) and 6 months following (outcome assessment) the study entry date. Using logistic regression, a model of the relationship between type of NSAID and mortality was produced controlling for other co-variables.

Databases. For over 30 years the Saskatchewan Department of Health has maintained administrative computer files of the insured health-related services for all members of the Saskatchewan Health Insurance Plan[32]. Over 99% of the approximately one million residents of the province are covered by the Plan and are assigned their own unique 9-digit personal health number[32]. This number is required to access services for all covered health-related activity and allows linkage across the various service databases (e.g., physician services, hospital services, and outpatient prescription drug services). The remaining 1% of the population are covered by federal health plans and are comprised of federal employees (e.g., military, RCMP), and inmates of federal correctional institutions. None of these groups are captured by the Saskatchewan Health databases.

All Saskatchewan Health beneficiaries are eligible for outpatient prescription drug benefits, except those who receive such benefits from the federal government (e.g., registered Indians). Approximately 91% of the covered population is eligible for drug plan benefits.

All physician visits, hospital discharges (including deaths), and drug prescriptions for insured services are captured and the databases have high validity and reliability as numerous studies have shown[33-35]. Data were provided in a non-identifiable format, so that no individual could be identified. The Ethical Review Board at the University of Saskatchewan approved the project.

Study NSAID. Nabumetone (Relafen®, Relifex®) was the first selective COX-II inhibitor to be listed in the Saskatchewan Formulary. It is a pro-drug that does not undergo enterohepatic recirculation, a feature that may reduce gastrointestinal side-effects. There is randomized controlled trial evidence of the improved gastrointestinal profile of nabumetone[24]. Arthrotec®, a combination pill consisting of diclofenac plus the gastroprotective agent misoprostol, was listed in the Saskatchewan Formulary in 1995. There is randomized controlled trial evidence of reduced ulceration with misoprostol added to NSAID as well as with Arthrotec® alone[22,23,36]. It was anticipated that these drugs may have a lower associated mortality, albeit by 2 slightly differing mechanisms: nabumetone reducing the loss of prostaglandins in the gastrointestinal tract and misoprostol replacing depleted prostaglandin E1. The diclofenac+ group consisted of participants who had filled a prescription for diclofenac in all its forms in 1995 and who also filled a separate prescription for a gastroprotective agent.

Gastroprotective agents in this case included sucralfate, misoprostol, the proton pump inhibitors, or one of the H2-blockers, some time in the 6 months before or after the signal prescription for diclofenac. Misoprostol, the proton pump inhibitors and high dose H2 blockers have all been shown in clinical trials to reduce the risk of serious gastrointestinal ulceration. However the need for 2 simultaneous medications might be expected to be less effective than a single-ingredient tablet or a single combination tablet, owing to decreased compliance. Finally naproxen continues to be one of the most popular NSAID and has been shown in other population based studies to confer heightened gastrointestinal risk[37]. It was selected as a measure of "usual" risk.

Participants. Using the Saskatchewan health-services databases individuals were identified at the time they first filled a prescription for one of the

4 study NSAID in 1995. The year 1995 was chosen because it was the first full year that all 4 drugs were listed in the Formulary. It was also the only full year in which all 4 drugs had unrestricted coverage.

Subjects were followed forward in time for 6 months from the date that the individual filled the prescription until death. Fact of death was collected through the health insurance registry but cause of death, although available in the vital statistics database, was not obtained. The physician, hospital, and outpatient prescription drug databases were examined retrospectively for 4 years prior to the signal prescription to collect physician, hospital, and outpatient prescription drug services history, as a measure of comorbidity. Subjects were therefore required to have had coverage for the previous 4 years. Demographic characteristics on each individual were also compiled.

Other prescriptions for non-study NSAID were allowed both before and after the entry into the study (we included a variable in the multivariate analysis to examine this "multiple NSAID" effect). However a prescription for more than one of the 4 study NSAID resulted in the exclusion of the individual from the analysis to preserve the integrity of the inception cohort.

Analysis. Descriptive analysis was performed, as well as appropriate bivariate analysis for potential predictor variables and the dependent variable, death. Associations at the $p \leq 0.25$ level were brought forward for multivariable modeling. A stepwise backward elimination logistic regression model of the relationship between the study NSAID and death was produced using the technique described by Hosmer and Lemeshow[38], with $p \leq 0.05$ required to enter the final model. Model fit was judged by the HL goodness-of-fit statistic and the Wald chi-square statistic. Interactions were sought but did not contribute to model fit.

RESULTS

In 1995 over 300,000 prescriptions for all Formulary NSAID were filled by more than 100,000 individuals (14% of the total eligible population) in Saskatchewan (from written data provided to authors from Saskatchewan Health). About 14% of the total prescriptions were for naproxen, 7% were for Arthrotec, 3% for diclofenac+ and 2% for nabumetone (from written data provided to authors from Saskatchewan Health). The study cohort consisted of 18,424 individuals who filled a prescription for one of the 4 study drugs in 1995. Data for the cohort were complete with no missing or out of range values.

Baseline characteristics between the groups taking different study NSAID were remarkably similar (Table 1). Characteristics were chosen based on known or suspected associations with NSAID or potential to cause mortality. No convincing clinical differences existed between groups, although statistically very low p values were obtained due to large sample sizes. The exceptions appear to be the younger age in the naproxen group and the higher rate of gastric and duodenal ulcers and hemorrhage with diclofenac+.

Crude mortality rates differed markedly between NSAID groups (Table 2). The nabumetone group experienced the lowest mortality followed by the Arthrotec®, diclofenac+, then naproxen groups. These differences in mortality are maintained in the final multivariate model (Table 3), with relatively few differences after adjustment. The odds of death for the diclofenac+ and naproxen groups are significantly higher than the nabumetone group. Because the risk of the outcome, death, is low and the numbers in the study high, the odds ratios (OR) will be a very good approximation of the relative risk. Hence the risk of death is 3 times higher in the naproxen group than in the nabumetone.

The stability of the final model was further tested by the deliberate misclassification of 10% of patients in the nabumetone group (randomly selected) being switched to the naproxen group and 10% of the naproxen group switched to the nabumetone. The OR obtained from this model varied by only 15.5% of the original and the statistical significance was almost identical. This indicates a very stable model.

Switching the referent NSAID group around in the model helps to show differences between individual NSAID (Table 4). Using this approach one can see that Arthrotec® has a significantly lower mortality than the diclofenac+ and naproxen groups though the magnitude of difference is not as great as that found with nabumetone (OR of 1.4 and 2.1 respectively). The diclofenac+ group has a significantly lower mortality than the naproxen group (OR of 1.5). There is no statistical difference between nabumetone and Arthrotec® although the trend suggests that nabumetone has the lower mortality.

DISCUSSION

There appears to be a dramatic difference in (all cause) mortality between nabumetone and naproxen. If the mortality rates for the nabumetone group were applied to the whole of the historical cohort (i.e., all 18,424 individuals instead of just the 2,241 who actually took nabumetone) then the expected number of deaths would have been 204 compared to 355 actually observed (151 presumably preventable deaths). Just comparing the crude death rates between nabumetone and naproxen one would have to switch 27 patients over to nabumetone (from naproxen), in order to prevent one death.

One might speculate that nabumetone has a lower mortality rate because of a lower side-effect profile. This may be related to its relative COX-II selectivity, or because it is a non-acidic pro-drug that doesn't undergo enterohepatic recirculation. The combination of an NSAID with a gastroprotective agent, misoprostol, also results in reduced mortality. This benefit is not seen when diclofenac is given as a tablet separate from anti-ulcer agents however. This may relate to reduced adherence when taking more than one drug, although we did not assess this in this analysis. We also acknowledge not all anti-ulcer agents are equally gastroprotective, and the beneficial effects of diclofenac and misoprostol might have been diluted in this group by the poorer performance of the H2 blockers and sucralfate. We have no way of knowing from these current data what the cause of death was and whether the rates of death from gastrointestinal causes differed between NSAID groups.

We observed the association of central nervous system drugs (defined as antidepressants, antipsychotics, anticon-

Table 1. Selected baseline characteristics (% unless otherwise stated) between 4 study NSAID groups, Saskatchewan, Canada, 1991–95 (n = 18,424).

	Nabumetone	Arthrotec	Diclofenac+	Naproxen	p
Sex, F:M ratio	1.9	1.6	1.5	1.8	< 0.0001
Age, yrs, median (IQR)	65 (50–75)	65 (50–80)	65 (50–75)	60 (45–75)	< 0.0001
Previous hospitalization	49.8	50.6	57.9	56.4	< 0.0001
Previous anticoagulation	5.1	5.3	5.8	4.5	NS
Previous corticosteroid use	14.5	12.4	15.4	15.6	< 0.0001
Previous NSAID use	77.9	72.3	85.7	79.3	< 0.0001
Hypertension	36.4	38.6	41.3	34.5	< 0.0001
Ischemic heart disease	18.6	19.0	22.3	19.6	< 0.0001
Heart failure	9	8.8	10.2	7.8	0.003
All cancers	9.2	9.1	10.0	10.9	0.002
Nephritis/nephrosis	1.1	1.2	1.6	1.5	NS
Diabetes mellitus	11.6	10.6	11.5	11.0	NS
Rheumatoid arthritis	8.1	5.5	7.2	6.5	< 0.0001
Gastric ulcer	2.1	1.6	2.5	2.3	< 0.0001
Duodenal ulcer	3.4	2.7	5.6	4.7	< 0.0001
GI hemorrhage	3.3	3.3	3.9	3.5	< 0.0001

IQR: interquartile range; NS: not significant.

Table 2. Crude 6 month mortality rates (deaths/1000 population/6 mo) for study NSAID groups, Saskatchewan, Canada, based on followup data between 1995 and 1996 (n = 18,424).

NSAID	Crude Mortality Rates (95% CI)	Crude Relative Risk (95% CI)	Age/Sex Adjusted Relative Risk (95% CI)
Nabumetone	11.3 (7.3–17.2)	1.0 (referent)	1.0 (referent)
Arthrotec	16.2 (11.4–22.4)	1.43 (0.94–1.70)	1.41 (0.9–2.2)
Diclofenac+	23.1 (17.0–30.4)	2.05 (1.32–3.12)	1.95 (1.2–3.1)
Naproxen	30.0 (23.1–38.2)	2.66 (1.70–4.02)	2.8 (1.8–4.4)

vulsants, narcotic analgesics, minor tranquilizers, sedatives, and hypnotics) and increased mortality in those individuals taking NSAID. In the final multivariate model (Table 3) we combined central nervous system drugs with 5 other variables, to improve the overall fit of the model. However, when we examined the central nervous system drugs alone (data not shown), an individual who filled a prescription for one or more of these medications was twice as likely to die than an individual who did not (OR 1.95, 95% confidence interval, CI, 1.5-2.6). This could be related to higher rates of suicide in this group or to the use of narcotic analgesia in palliative care. Interestingly Garcia-Rodriguez and colleagues have suggested that antidepressants are associated with gastrointestinal bleeding[39]. However, since we do not have cause-specific mortality data, we cannot conclude with certainty that our data would concur. This finding needs further study, given the widespread use of these drug classes in the general population.

Adjustment for other factors known to affect the risk for NSAID related gastrointestinal morbidity did not influence the estimates or risk much at all in this large population based study. We were able to measure a very large number

Table 3. Adjusted odds ratio (OR) in the final multivariate model of NSAID group versus all cause mortality (n = 18,424), Saskatchewan, 1995. The predictors in the multivariable model have been adjusted for all other factors in the model. Comorbidities include central nervous system drugs, hospitalization, heart failure, stroke, cancer, or renal diseases in the 4 years prior to the study.

Variable Description	Adjusted OR	95% CI Lower	95% CI Upper
Nabumetone*	1.00	—	—
Arthrotec	1.39	0.90	2.14
Diclofenac +	1.96	1.25	3.07
Naproxen	2.95	1.88	4.62
Female sex	0.54	0.43	0.67
Musculoskeletal disorders	0.64	0.50	0.83
Age			
0–39 yrs	1.00	—	—
40–44 yrs	10.6	2.30	49.1
45–49 yrs	11.0	2.44	49.5
50–54 yrs	19.3	4.51	82.8
55–59 yrs	13.8	3.18	59.9
60–64 yrs	18.8	4.45	79.0
65–69 yrs	16.6	3.92	69.9
70–74 yrs	22.8	5.49	94.6
75–79 yrs	43.9	10.8	179
80–84 yrs	48.8	11.9	200
85+ yrs	122	30.2	494
Comorbidity	6.4	3.5	11.7

* Reference category. Hosmer-Lemeshow goodness of fit: 0.723; Wald chi-square for Arthrotec: 2.2 (p = 0.138), diclofenac+: 8.7 (p = 0.003), and naproxen: 22.2 (p < 0.001).

of proxy measures for comorbidity (diagnostic codes, drug prescriptions, hospitalizations, etc.) and control for these in the multivariate statistical analysis. Our results are unlikely then to be confounded by systematic differences in overall health status of the 4 groups. It is possible that the nabume-

Table 4. Adjusted OR (95% CI) for NSAID group versus mortality alone (with each NSAID alternately used as the reference group), Saskatchewan, 1995 (n = 18,424).

Comparison NSAID Group	Reference NSAID Group: Nabumetone (n = 2241)	Arthrotec® (n = 8550)	Diclofenac+ (n = 4336)	Naproxen (n = 3297)
Nabumetone	1.0	0.7 (0.5–1.1)	0.5 (0.3–0.8)*	0.3 (0.2–0.5)*
Arthrotec	1.4 (0.9–2.1)	1.0	0.7 (0.5–0.9)*	0.5 (0.4–0.6)*
Diclofenac+	2.0 (1.3–3.1)*	1.4 (1.1–1.8)*	1.0	0.7 (0.5–0.9)*
Naproxen	3.0 (1.9–4.6)*	2.1 (1.6–2.8)*	1.5 (1.1–2.0)*	1.0

* Statistically significant difference ($p < 0.01$) between comparison NSAID and reference NSAID.

tone group had less severe illness than the other groups, but again this seems unlikely and we feel the range of comorbidity measures we used would have controlled for this. We could not control for unmeasured factors, notably socioeconomic status.

This was not a true incident cohort of NSAID users, as we did not exclude those who may have used the study drugs prior to 1995; nor could we be sure that the individual took the drugs actually dispensed. In this analysis we did not control for drug strength or regime. It is probable that some individuals in the study also took a gastroprotective agent; however, as for most of these factors, we think it unlikely that this would have resulted in systematic bias between individual study groups. It seems unlikely that one NSAID group experienced this type of misclassification bias any more or less than the other NSAID groups. We also did not validate our measures of comorbidity (the aim of our study was not to investigate the relationship of specific comorbidities on mortality). However it does not seem that the 4 groups differed systematically in comorbid conditions, as shown in Table 1.

In conclusion, nabumetone, and to a lesser extent Arthrotec, appear to cause significantly less mortality than diclofenac (plus a separate gastroprotective) or naproxen. The reasons for this are unclear but merit further study.

ACKNOWLEDGMENT

Dominique Ibanez helped with datafiles. Dr. Leonard Tan gave helpful advice on earlier drafts of the manuscript.

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