# Risk of Hospitalization with Peptic Ulcer Disease or Gastrointestinal Hemorrhage Associated with Nabumetone, Arthrotec®, Diclofenac, and Naproxen in a Population Based Cohort Study

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***ABSTRACT.*** ***Objective.*** To identify the unbiased differences in the risk of hospitalization with peptic ulcer disease (PUD) or gastrointestinal (GI) hemorrhage among populations using 4 nonsteroidal antiinflammatory drugs (NSAID): nabumetone, Arthrotec®, diclofenac plus a cytoprotective agent dispensed separately (diclo+coRx), and naproxen.

***Methods.*** A population based historical cohort study using linked data from provincial healthcare databases. The population of the province of Saskatchewan, Canada, entitled to drug plan benefits in 1995 was eligible (roughly 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 for 6 months to determine outcomes. Logistic regression was used to produce estimates of the risk of admission to hospital with a primary diagnosis of PUD or GI hemorrhage associated with the study drugs unbiased by known confounders.

***Results.*** Compared to Arthrotec the adjusted odds of hospitalization for PUD for participants taking nabumetone was 2.6 (95% CI 1.0–6.6), diclo+coRx 6.8 (95% CI 3.5–13.4), and naproxen 7.9 (95% CI 3.9–15.9). Compared to nabumetone the adjusted odds of hospitalization for PUD for participants taking diclo+coRx was 2.7 (95% CI 1.2–6.0) and naproxen 3.1 (95% CI 1.3–7.1). No significant differences were noted in terms of admissions for GI hemorrhage.

***Conclusion.*** Participants taking nabumetone and Arthrotec had significantly lower risk of hospitalization for PUD than those taking the other study drugs. Arthrotec was superior to nabumetone in a head to head comparison and especially when compared with the diclo+coRx and naproxen groups. No short term differences were seen in the rates of admission for GI hemorrhage. It appears that inherent gastroprotective strategies with Arthrotec and to a lesser extent with nabumetone do translate into decreased serious GI side effects at the population level in the short term. (J Rheumatol 2005;32:2212–7)

*Key Indexing Terms:*
NONSTEROIDAL ANTIINFLAMMATORY DRUGS PEPTIC ULCER DISEASE
GASTROINTESTINAL HEMORRHAGE DICLOFENAC ARTHROTEC

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Nonsteroidal antiinflammatory drugs (NSAID) are one of the most commonly prescribed classes of drugs[1]. Over 300,000 prescriptions were dispensed in Saskatchewan, Canada, in 1995 to 14% of the total eligible population (data 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 subtypes of NSAID are available, each with 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 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) to peptic ulceration, hemorrhage, and death. Adverse events are magnified by the overrepresentation 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 age 65 years is as high as 90%[21], while in the province of Saskatchewan in 1995, this figure was about 55% (data from Saskatchewan Health).

A number of pharmacological efforts have been made over the past decade to reduce NSAID side effects, including enteric coating tablets, parenteral administration, and formulation of prodrugs designed to bypass absorption in the upper GI tract. 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 fixed-dose 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]. The most recently developed NSAID selectively block 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-1 and COX-2, and hence while they are effective antiinflammatory agents they also cause GI damage. A drug that selectively blocks the activity of COX-2 will theoretically produce an antiinflammatory effect without GI 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 prodrug that may also have some intermediate COX-2 selectivity. More recently, COX-2 specific NSAID have been marketed, such as celecoxib and rofecoxib, that have greater selectivity/specificity for the COX-2 enzyme.

While the efficacy of some of these approaches in reducing GI morbidity was established through a number of randomized controlled trials[22-24], the actual effectiveness of these approaches in the general population of NSAID users is far from clear. Randomized trials tend to be performed on highly selected groups who experience unusually intense medical scrutiny and followup. The generalizability of the study findings to the real world can therefore be problematic[25]. We previously showed that nabumetone and Arthrotec have significantly lower all-cause mortality than diclofenac (prescribed in association with an "anti-ulcer" drug) and naproxen in the Saskatchewan population, suggesting that some of these protective measures may translate into benefits at the population level[26]. We did not collect cause of death data in that study, however, and so we could not tell if the reduction in mortality came from a drop in deaths that might have been from possible NSAID related side effects. For these reasons we wanted to observe what the level of serious possible NSAID related side effects would be on an unselected, complete population of NSAID users.

## MATERIALS AND METHODS

The study 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 determine health related services for 4 years prior to (comorbidity) and 6 months following (outcome assessment) the study entry date. Using logistic regression, a model of the relationship between type of NSAID and subsequent hospitalization with a primary discharge diagnosis of peptic ulcer disease (PUD) or GI hemorrhage was produced controlling for other known covariables.

*Databases*. For over 30 years the Saskatchewan Department of Health has maintained administrative computer files of insured health-related services for all members of the Saskatchewan Health Insurance Plan[27]. Over 99% of about 1 million residents of the province are covered and are assigned their own unique 9-digit personal health number[27]. This number is required to access insured services 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 is covered by federal government health plans and comprises federal employees (e.g., military, RCMP) and inmates of federal correctional institutions. None of these groups are recorded 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 Native Canadians). About 91% of the covered population is eligible for drug plan benefits.

All physician visits, hospital separations, and drug prescriptions for insured services are recorded, and the databases have high validity and reliability[28-30]. Data were provided in a non-identifiable format, such that no individual could be identified. The Ethical Review Board approved the project at the University of Saskatchewan.

*Study NSAID*. Nabumetone (Relafen®, Relifex®) is a prodrug that does not undergo enterohepatic recirculation, a feature that may reduce GI side effects. There is randomized controlled trial evidence of the improved GI profile of nabumetone[24]. Arthrotec, a fixed-dose combination tablet consisting of diclofenac plus the gastroprotective agent misoprostol, was listed in the Saskatchewan Formulary in 1995 (in 1995 only the diclofenac 50 mg combination was available). There is randomized controlled trial evidence of reduced ulceration with misoprostol added to NSAID as well as with Arthrotec alone[22,23,31]. It was anticipated that these drugs would lower associated PUD, albeit by 2 slightly differing mechanisms — nabumetone reducing the loss of prostaglandins in the GI tract and misoprostol replacing depleted prostaglandin $E_1$. The diclofenac plus cytoprotective agent (diclo+coRx) group consisted of participants who had filled a prescription for diclofenac in any form in 1995 and who also filled a separate prescription for a gastroprotective agent some time in the 6 months before or after the signal prescription for diclofenac. Gastroprotective agents in this case included sucralfate, misoprostol, the proton pump inhibitors, or one of the $H_2$ blockers. Misoprostol has been shown in clinical trials to reduce the risk of serious GI ulceration. Although proof is lacking, the proton pump inhibitors and high-dose $H_2$ blockers are prescribed with the hope they may reduce GI side effects also. 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 GI risk[32]. 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. Nabumetone was moved to restricted coverage in July 1996.

Subjects were followed forward in time for 6 months from the date that the individual filled the prescription. Any admissions to hospital where the primary discharge diagnosis, according to ICD-9 code, was PUD (gastric ulcer, duodenal ulcer, or peptic ulcer site unspecified) or GI hemorrhage were identified. 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 entry into the study (we included a simple dichotomous 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 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, hospitalization with PUD. Associations at the $p \leq 0.25$ level were retained for multivariable modeling. A stepwise logistic regression model of the relationship between the study NSAID and death was produced using the technique described by Hosmer and Lemeshow[33], with $p \leq 0.05$ required to enter the final model. Model fit was judged by the Hosmer-Lemeshow goodness-of-fit statistic, the Wald chi-square statistic, and classification tables. Interaction effects were examined, and if significant were included in the final model.

## RESULTS

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. 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 previous gastric and duodenal ulcers and hemorrhage with diclo+coRx.

The crude rates of hospitalization for PUD (Table 2) show that the rates of hospitalization for the Arthrotec and nabumetone groups are significantly lower (0.2% and 0.4%, respectively) than those for the diclo+coRx and naproxen groups (1% for both).

The crude rates of hospitalization for GI hemorrhage (Table 3) show that while there is a suggestion that the rates are lower for nabumetone and Arthrotec (0.0% and 0.1%, respectively) versus diclo+coRx and naproxen (0.3% and 0.2%, respectively), this does not reach statistical significance. Given the lack of statistical significance for GI hemorrhage at the bivariate level, a multivariate model was not constructed for this outcome.

The final multivariate model (Table 4) showed that compared to Arthrotec the adjusted odds of hospitalization for PUD for participants taking nabumetone was 2.6 (95% CI 1.0–6.6), for diclo+coRx 6.8 (95% CI 3.5–13.4), and for naproxen 7.9 (95% CI 3.9–15.9). Compared to nabumetone the adjusted odds of hospitalization for PUD for participants taking diclo+coRx was 2.7 (95% CI 1.2–6.0) and for naproxen 3.1 (95% CI 1.3–7.1) (data not shown).

As a test of the stability of the model the entire analysis was rebuilt excluding the diclo+coRx participants entirely. We considered the diclo+coRx group to potentially be the most heterogeneous of all (given the wide range of potential "cytoprotectives" they might have taken). Results were similar to those obtained when the diclo+coRx group was

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

| | Nabumetone | Arthrotec® | Diclo+coRx | Naproxen | Significance |
|---|---|---|---|---|---|
| Sex (F:M) | 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 |
| Previous cancer (all) | 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 |
| Previous gastric ulcer | 2.1 | 1.6 | 2.5 | 2.3 | < 0.0001 |
| Previous duodenal ulcer | 3.4 | 2.7 | 5.6 | 4.7 | < 0.0001 |
| Previous GI hemorrhage | 3.3 | 3.3 | 3.9 | 3.5 | < 0.0001 |

IQR: interquartile range, NSAID: nonsteroidal antiinflammatory drug, NS: not significant, GI: gastrointestinal.

*Table 2*. Crude hospitalization rates for peptic ulcer disease between 4 study NSAID groups, Saskatchewan, Canada, 1995 (n = 18,424).

| Study Drug | Total No. of Study Drug Users | No. Hospitalized Over 6 mo (% of total) | Extrapolated Hospitalization Rate (% of NSAID users/yr) |
|---|---|---|---|
| Arthrotec | 8,550 | 18 (0.2) | 0.4 |
| Nabumetone | 2,241 | 10 (0.5) | 0.9 |
| Diclo+coRx | 4,336 | 44 (1.0) | 2.0 |
| Naproxen | 3,297 | 34 (1.0) | 2.0 |
| Total | 18,424 | 106 | 1.2 |

*Table 3*. Crude hospitalization rates for GI hemorrhage between 4 study NSAID groups, Saskatchewan, Canada, 1995 (n = 18,424).

| Study Drug | Total No. of Study Drug Users | No. Hospitalized Over 6 mo (% of total) | Extrapolated Hospitalization Rate (% of NSAID users/yr) |
|---|---|---|---|
| Arthrotec | 8,550 | 10 (0.1) | 0.2 |
| Nabumetone | 2,241 | 1 (0.0) | 0.1 |
| Diclo+coRx | 4,336 | 11 (0.3) | 0.5 |
| Naproxen | 3,297 | 5 (0.2) | 0.3 |
| Total | 18,424 | 27 | 0.3 |

*Table 4*. Adjusted* odds ratios for variables in the final multivariate model estimating risk of hospitalization for peptic ulcer disease (n = 18,424), Saskatchewan, 1995.

| Variable Description | Adjusted OR | 95% CI | |
|---|---|---|---|
| | | Lower | Upper |
| Arthrotec** | | — | — |
| Nabumetone | 2.6 | 1.0 | 6.6 |
| Diclo+coRx | 6.8 | 3.5 | 13.4 |
| Naproxen | 7.9 | 3.9 | 15.9 |
| Female sex, yrs | 0.6 | 0.4 | 0.9 |
| 0–64** | | — | — |
| 65–69 | 2.5 | 1.3 | 4.9 |
| 70–74 | 2.1 | 1.0 | 4.3 |
| 75–79 | 3.9 | 2.1 | 7.2 |
| 80–84 | 6.1 | 3.4 | 10.9 |
| 85+ | 5.2 | 2.7 | 10.0 |
| Previous hospitalization | 2.4 | 1.5 | 4.0 |
| Previous chronic liver disease | 4.4 | 1.3 | 15.1 |
| Previous disease of blood | 1.7 | 1.1 | 2.7 |
| Previous peptic ulcer disease | 1.4 | 0.5 | 3.6 |
| Previous cancer (all) | 2.1 | 0.6 | 7.2 |
| Previous hospitalization × previous cancer (all)*** | | | |
| NSAID × previous PUD*** | | | |

Hosmer-Lemeshow goodness of fit = 0.34, Wald chi-square for Arthrotec 41.0 ($p \leq 0.0001$), classification 99.4%. * The predictors in the multivariable model have been adjusted for all other factors in the model. ** Reference category. *** Interaction terms. PUD: peptic ulcer disease.

included: Compared to Arthrotec the adjusted odds of hospitalization for PUD for participants taking nabumetone was 2.1 (95% CI 1.0–4.7) and for naproxen 4.7 (95% CI 2.6–8.4).

Because the risk of the outcome is low and the numbers in the study high, the odds ratios will be a very good approximation of the relative risk. Hence the risk of hospitalization with PUD is almost 8 times higher in the naproxen group than in the Arthrotec group (and could be as much as 16 times higher).

In addition to the risk conferred by the NSAID investigated in this study we found several other factors significantly associated with higher risk for hospitalization: men were 70% more likely than women to have been admitted to hospital (OR 1.7, 95% CI 1.1–2.5), those who were 85 years or older 5 times more likely than those under age 65 to have

been admitted, and those who had experienced prior hospitalization (OR 2.4, 95% CI 1.5–4.0) or had chronic liver disease (OR 4.4, 95% CI 1.3–15.1) or had any blood-related disease (OR 1.7, 95% CI 1.1–2.7) were more likely to have been hospitalized than those who did not have one of these conditions.

## DISCUSSION

There seems to be a difference in the risk of hospitalization for peptic ulcer disease between the NSAID groups. In particular, Arthrotec appears to be safer than all the other 3 NSAID, with large risk reductions compared to diclo+coRx and naproxen. Nabumetone also appears to be safer than diclo+coRx and naproxen, although less dramatically than observed with Arthrotec. Arthrotec is safer when compared directly with nabumetone. If the hospitalization rates for the Arthrotec group were applied to the whole of the historical cohort (i.e., all 18,424 individuals instead of just 8,550 who actually took Arthrotec), then only 39 patients would have been hospitalized, compared to 106 actually observed (67 presumably preventable admissions) over a 6 month period. Just using the crude rates for Arthrotec and naproxen, one would have to switch 120 patients over to Arthrotec (from naproxen) in order to prevent one hospital admission for PUD.

The rates of GI hemorrhage were also lower in the nabumetone and Arthrotec groups, especially the nabumetone group. This did not reach statistical significance, however, possibly because the event rate was so low for this complication (there were only 27 hospital admissions for GI hemorrhage in more than 9,200 person-years of observation). Of interest, 4 out of the 27 individuals died.

One might speculate that nabumetone has a lower peptic ulcer rate because of its relative COX-2 selectivity (although the evidence for this is weak), or because it is a nonacidic prodrug that does not undergo enterohepatic recirculation. Arthrotec is a fixed-dose combination of an NSAID (diclofenac) with a gastroprotective agent, misoprostol. The diclo+coRx group in part represents individuals who are taking diclofenac and misoprostol separately, a strategy that may well result in lower compliance and therefore lower efficacy than taking a combination pill (such as Arthrotec). Also, any beneficial effects from misoprostol may well have been watered down by the poor (or nonexistent) effects from other coprescribed drugs such as the $H_2$ blockers and sucralfate.

Adjustment for other factors known to affect the risk for NSAID related GI morbidity did not influence the estimates or risk much at all in this large population based study (the crude rates were about 2.5–5 times higher in the diclo+coRx and naproxen groups). We were able to measure a very large number of proxy measures for comorbidity (diagnostic codes, drug prescriptions, hospitalizations, etc.) and control for these in the multivariate statistical analysis. The results of this study are unlikely then to be confounded by systematic differences in overall health status of the 4 groups. Of course 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 they were 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 that we were not able to measure; 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 would have experienced misclassification bias any more or less than the other NSAID groups. We also did not validate our measures of comorbidity because the aim of this study was not to investigate the relationship of specific comorbidities on hospitalization rates. But again the effect of this potential weakness should have been similar for each of the 4 NSAID groups.

Results of previous clinical trials showing reduced gastrointestinal side effects from nabumetone and Arthrotec do translate into reduced hospitalization for peptic ulcer disease at the population level when compared with diclo+coRx and naproxen.

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