American Journal of Gastroenterology
© 2008 by Am. Coll. of Gastroenterology
Published by Blackwell Publishing

ISSN 0002-9270
doi: 10.1111/j.1572-0241.2008.01811.x

Hospitalizations for Upper and Lower GI Events Associated With Traditional NSAIDs and Acetaminophen Among the Elderly in Quebec, Canada

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BACKGROUND: The risk of upper/lower gastrointestinal (GI) adverse events associated with the concomitant use of traditional nonsteroidal anti-inflammatory drugs (tNSAIDs) with acetaminophen has not been assessed. Among users of these drugs, the concomitant use of proton pump inhibitors (PPIs) with tNSAIDs may reduce the risk of upper GI adverse events, but its effect on lower GI events is not clear.

OBJECTIVE: To compare the rates of GI hospitalization (ulceration, perforation, or bleeding in the upper or lower GI tract) among elderly patients taking tNSAIDs or the combination of a tNSAID and acetaminophen with and without a PPI *versus* those taking acetaminophen alone.

METHODS: We conducted a population-based retrospective cohort study using data obtained from the government of Quebec health insurance agency databases and the hospital discharge summary database. Patients of 65 yr of age or older who filled a prescription for acetaminophen or a tNSAID between January 1998 and December 2004 were entered in the cohort at the date of the first filled prescription from either of these medications (index date). Follow-up ended at the first date of a GI hospitalization, death, or the end of the study period.

RESULTS: The cohort included 644,183 elderly patients. These patients received 1,778,541 prescriptions for tNSAIDs (315,222, 17.7% with a PPI), 158,711 for the combination of a tNSAID and acetaminophen (40,797, 25.7% with a PPI), 1,597,725 for acetaminophen (>3 g/day) (504,939, 31.6% with a PPI), and 3,641,140 for acetaminophen (≤3 g/day) (1,031,939, 28.3% with a PPI). Using Cox regression models that adjusted for time-dependent variables (aspirin, anticoagulants, and clopidogrel) and other fixed patient baseline characteristics, we found similar risks of GI hospitalizations among time periods when patients were exposed to either a tNSAID with a PPI, acetaminophen (>3 g/day) with a PPI, or acetaminophen (≤3 g/day) with a PPI. The risk of GI hospitalization among users of PPIs during exposure to the combination of acetaminophen with a tNSAID was twice as high as that of the reference category, acetaminophen (≤3 g/day) without a PPI (hazard ratio [HR] 2.15, 95% confidence interval [CI] [1.35–3.40]). Among nonusers of PPIs, the risk of GI hospitalization was 1.20 (1.03–1.40) during exposure to acetaminophen (>3 g/day), 1.63 (1.44–1.85) during exposure to tNSAIDs, and 2.55 (1.98–3.28) during exposure to the combination of a tNSAID and acetaminophen compared with the reference category.

CONCLUSION: Among elderly patients requiring analgesic/anti-inflammatory treatment, use of the combination of a tNSAID and acetaminophen may increase the risk of GI bleeding compared with either agent alone.

(Am J Gastroenterol 2008;103:872–882)

INTRODUCTION

The concern that cyclooxygenase (COX)-2 inhibitors may increase the risk of cardiovascular events has prompted some patients to look for alternative treatments to control their pain. Possible strategies are the use of traditional nonsteroidal anti-inflammatory drugs (tNSAIDs), acetaminophen, or a combination of acetaminophen with tNSAIDs (1). Practice guidelines recommend acetaminophen (up to 4 g/day) as initial therapy for the management of osteoarthritis (OA) pain (2–6). Acetaminophen has been traditionally considered a gastrointestinally (GI) safer alternative to tNSAIDs (7).

Acetaminophen use at the doses most commonly prescribed has not been associated with upper GI complications (8). However, based on a limited number of studies, the use of higher doses of acetaminophen may be associated with upper GI events (8, 9). This association remains unclear and needs to be investigated further. In addition, the effect of acetaminophen at either high or regular doses on the lower GI tract has not been studied.

The evidence to date suggests that tNSAIDs are superior to acetaminophen and may be preferred by patients for controlling moderate-to-severe OA pain (7, 10, 11). The association between tNSAIDs and upper GI adverse events is well documented (12). Epidemiologic studies suggest that tNSAIDs may also increase the risk of GI adverse events in the lower GI tract, including ulceration (with possible resulting obstruction), bleeding, diverticulitis, and perforation (13–18). The coprescription of gastroprotective agents (GPA) (misoprostol, proton pump inhibitors [PPIs], and double doses of histamine-2 receptor antagonists [H_2RAs]) with tNSAIDs may reduce the risk of tNSAID-related upper GI events (19–21) and has been recommended by Canadian and American clinical practice guidelines for patients at risk of these events (2–6). However, the effect of concomitant utilization of a GPA with tNSAIDs in preventing GI bleeding in the lower GI tract is not clear.

The risk of upper GI adverse events with tNSAIDs increases with tNSAID dose and number of concomitant tNSAIDs used (2–6). The combination of a tNSAID with acetaminophen is a possible alternative to prescribing higher doses of tNSAIDs or a combination of two tNSAIDs, but the GI safety of the combination of a tNSAID with acetaminophen has not been examined.

We assessed the association between tNSAIDs, acetaminophen at doses $\leq$3 g/day, acetaminophen at doses $>$3 g/day, and the combination of a tNSAID with acetaminophen and hospitalizations for upper or lower GI events among elderly patients in Quebec, Canada. The risks of upper and lower GI events were assessed separately and in combination. Assessments were made when the studied medications were used in combination with a PPI and when they were used without a PPI, respectively. Among the GPAs, the PPIs have been the most widely used in Quebec (22).

METHODS

Data Sources

In Quebec, Canada, all persons aged 65 yr and older are eligible for coverage for prescription drugs and inpatient and outpatient physician services under the Provincial Health Care Fund administered by the Régie de l'Assurance Maladie du Québec (RAMQ). RAMQ administrative databases include demographic data, physician billings, and pharmacy records. In addition, hospital discharge summary data, Maintenance et Exploitation des Données pour l'Étude de la Clientèle Hospitalière (Med-Echo), maintained by RAMQ are available and include information on admission and discharge dates, principal and up to 15 secondary diagnoses, and procedures done during hospitalization for all Quebec residents.

Study Design

We conducted a population-based retrospective cohort study using demographics, physician billings, prescription drugs, and hospitalization records obtained from the RAMQ and Med-Echo databases of all persons aged 65 yr and older who received at least one dispensation for a tNSAID or acetaminophen during the period from January 1997 to July 2004.

Permission from the Government of Quebec Ethics Committee, the Commission d'Accès à l'Information, was obtained to link encrypted RAMQ and Med-Echo data.

Outcomes Definition

Hospitalizations for upper GI events were those occurring in either the stomach or the duodenum. They were identified from the hospital discharge summary database by a primary discharge diagnosis of ulceration, perforation, or bleeding in the upper GI tract (International Classification of Disease [ICD] codes 531.x, 532.x, 533.x, 534.x, 535.01, 535.31, 578.0, 578.1, 578.9, 537.83). Hospitalizations for lower GI events were those occurring in either the small intestine (beyond the duodenum) or the colon/rectum. They were identified from the hospital discharge summary database by a primary discharge diagnosis of gross rectal bleeding, lower GI perforation, ulceration, or diverticulitis with hemorrhage (ICD-9 codes 562.02, 562.03, 562.12, 562.13, 569.3, 569.41, 569.85, 569.83, 569.82).

Inclusion/Exclusion Criteria

Patients with a prescription for a tNSAID or acetaminophen between January 1998 and July 2004 were considered for inclusion at the date of their first filled prescription for these drugs during that period (index date). All included patients had at least 365 days of data prior to their index date. Diclofenac sodium/misoprostol (Arthrotec^{TM}, Pfizer Global Pharmaceutical, Kirkland, Canada) was not considered for inclusion as this combination includes the GPA misoprostol. Patients with upper/lower GI hospitalizations in the year prior to the index date and patients with a previously diagnosed cancer were excluded.

Follow-Up

All patients were followed up from their index date to the earliest of an upper/lower GI hospitalization, death, or the end of the study period (December 2004).

Exposure to tNSAIDs and Acetaminophen

The number of days of supply for each tNSAID or acetaminophen prescription was ascertained from the RAMQ database. For study purposes, "exposure" to acetaminophen/tNSAIDs was defined to be 1.25 $\times$ (number of days supplied) because GI adverse events with tNSAIDs may occur some time after the actual exposure period. Most

prescriptions for tNSAIDs and acetaminophen in Quebec are dispensed with a medication supply for 30 days or less (23, 24). Extending the exposure period by a grace period of 25% of the number of supplied days implies that, for most prescriptions, GI hospitalizations that occurred during therapy or up to 1 week immediately following that therapy would be attributed to tNSAID/acetaminophen use. This exposure definition was examined in sensitivity analyses, as described below. Consecutive days of exposure to the same medication were termed exposure episodes to that medication. Eight exposure episode categories were defined according to the drug(s) supplied: tNSAIDs only, acetaminophen ($\leq$3 g/day) only, acetaminophen (>3 g/day) only, acetaminophen ($\leq$3 g/day) with a PPI, acetaminophen (>3 g/day) with a PPI, a tNSAID with a PPI, a tNSAID and acetaminophen only, and a tNSAID and acetaminophen with a PPI. An exposure episode was classified as the combination of a tNSAID with acetaminophen if both agents were dispensed at the same date, otherwise the second drug dispensed was assumed to replace the first. For example, if acetaminophen was dispensed on a date following but during a tNSAID exposure episode, then exposure to the tNSAID was truncated at the date acetaminophen was dispensed and an exposure episode for acetaminophen was started. This rule was also examined in a sensitivity analysis as described below. An exposure episode was classified as a tNSAID with a PPI if an exposure episode for a PPI overlapped the exposure episode for a tNSAID by any number of days. Exposure episodes to acetaminophen with a PPI and those to the combination of a tNSAID and acetaminophen with a PPI were defined similarly. Patients could have contributed to more than one exposure category during the study period.

Patient Baseline Characteristics

The following baseline characteristics were extracted from the databases: age, sex, medications prescribed in the year prior to index date (corticosteroids, anticoagulants, antihypertensive or antidiabetic agents, aspirin, or clopidogrel), GI medical care or events that occurred in the year prior to the index date (lower or upper GI investigations, visits to gastroenterologists, diagnoses [ICD-9 codes] of lower or upper GI events, and the use of a PPI, misoprostol, or an H_2RA), concurrent chronic diseases that may be associated with GI events, inferred using ICD-9 codes from the physician billing database in the year prior to the index date (alcohol and drug abuse and/or use of naltrexone [treatment of alcohol or drug addiction], heart disease, renal insufficiency, liver disease, and chronic obstructive pulmonary disease), and use of any NSAID (tNSAIDs, COX-2 inhibitors, or meloxicam) or acetaminophen in the year prior to the index date.

Time-Dependent Patient Characteristics

Concurrent exposures to prescription medications that increase bleeding risk when used with tNSAIDs (aspirin, clopidogrel, and anticoagulants) were assessed at the beginning of every exposure episode to account for initiating or stopping these medications during follow-up.

Statistical Analyses

ASSESSING PATIENT BASELINE CHARACTERISTICS AND tNSAID AND ACETAMINOPHEN UTILIZATION IN FOLLOW-UP. Means and standard deviations (SD), medians and interquartile ranges, or proportions were used as appropriate to report patient characteristics at the index date. Patient characteristics at the index date were assessed by study drug received at that date. The proportions of patients who switched to a different exposure category in follow-up were also determined. The total number of prescriptions dispensed during follow-up as well as the total number of days supplied were assessed. Proportions of total days of PPI supply within each tNSAID/acetaminophen exposure episode were also determined.

ASSESSING GI HOSPITALIZATION OCCURRENCE. Unadjusted rates of GI hospitalizations per 1,000 patient-years (p-yr) were reported for each exposure category by dividing the total number of GI hospitalizations occurring in that category by the total number of exposure years within the category and multiplying by 1,000. Hospitalizations for upper GI events, lower GI events, and combined upper/lower GI events were determined separately. The hazard rates of GI hospitalizations were compared among the exposure categories using multivariable Cox regression models with time-dependent variables (25). In this analysis, exposure to study drugs, as well as use of aspirin, clopidogrel, or anticoagulants, varied with time as described previously. Univariate analyses were used to select potential confounders. Independent variables that were statistically significant in the univariate analyses at the 0.25 level (P value < 0.25) were entered in the model. An independent variable was kept in the model if it was statistically significant at the 5% level or if its exclusion caused more than a 10% change in the parameter estimate of any of the exposure categories.

SUBGROUP ANALYSES. Four subgroup analyses were conducted: (a) Cox regression models with time-dependent variables were constructed as described previously, but included only those patients without dispensation for any NSAID (either COX-2 inhibitors, meloxicam, or tNSAIDs) or acetaminophen in the year prior to the index date ("new users"). (b) Similar models were constructed including patients without any GI event in the previous year (dispensation for a PPI, misoprostol, an H_2RA, or HP-Pac (Abbott Laboratories, St. Laurent, Canada), visits to gastroenterologists, upper or lower GI investigations, and diagnoses with GI ulcers). (c) Similar models were also constructed including new users but further restricted to those without GI events in the previous year. (d) Finally, similar models were constructed in the subgroup of patients who had either an OA or rheumatoid arthritis (RA) diagnosis in the year prior to the index date.

SENSITIVITY ANALYSES. To assess the robustness of results, definitions of exposure and outcome were varied in four sensitivity analyses. In the main analysis, if a patient switched medication during the relevant exposure episode, an outcome was attributed to the last drug prescribed (*i.e.*, the drug to which the patient switched). In the first sensitivity analysis, the impact of the above assumption on the results was tested by attributing the GI hospitalization to the medication from which the patient switched. In the second sensitivity analysis, follow-up was terminated at the date of the first switch to another study medication and all analyses were repeated. The third and fourth sensitivity analyses considered all GI hospitalizations that occurred within 150% and 100% of the supplied days, respectively (as opposed to within 125% of the days supplied in the main analysis).

ADDITIONAL ANALYSES. Current tNSAID and acetaminophen utilization may differ from that of our study period (1998–2004) because of the change in knowledge about a possible association between some NSAIDs and cardiovascular events. In another study, using the same data, we found that the utilization of aspirin concurrently with tNSAIDs increased from 11% in 2000 to 17% in 2004 and from 20 to 30% with acetaminophen during the same time period (26). To examine the change in tNSAID and acetaminophen utilization that may have occurred during the study period, we assessed the total number of prescriptions from each exposure category from October 2004 to December 2004 (3-month period following rofecoxib withdrawal) in comparison to those of the same periods of the previous years, 2002 and 2003. All statistical analyses were performed using SAS version 9.1 for UNIX (SAS Institute, Inc., Cary, NC).

RESULTS

Patient Characteristics at Index Date

The cohort included 644,183 elderly patients, among whom 241,717 received tNSAIDs at the index date (24,279 [10.0%] received it in combination with a PPI), 15,595 received the combination of a tNSAID and acetaminophen (2,002 [12.8%] in combination with a PPI), 99,903 received acetaminophen >3 g/day (15,664 [15.7%] in combination with a PPI), and 286,968 received acetaminophen ≤ 3 g/day (24,279 [8.5%] in combination with a PPI). Overall, patients who received acetaminophen at the index date either alone or in combination with a PPI were less likely to have OA/RA, more likely to be male, more likely to be 80 yr of age or older, more likely to have other concomitant diseases, and more likely to have used prescription aspirin, anticoagulants, clopidogrel, or corticosteroids concomitantly compared with patients who received tNSAIDs at the index date either alone or in combination with acetaminophen (Table 1).

tNSAID and Acetaminophen Utilization in Follow-Up

The total number of prescriptions dispensed for the cohort during the study period included: 1,778,541 for a tNSAID (315,222 [17.7%] with a PPI), 158,711 for the combination of a tNSAID and acetaminophen (40,797 [25.7%] with a PPI), 1,597,725 for acetaminophen >3 g/day (504,839 [31.6%] with a PPI), and 3,641,140 for acetaminophen ≤3 g/day (1,031,939 [28.3%] with a PPI) (Table 2). As stated before, exposure episodes of tNSAIDs, acetaminophen, and the combination of a tNSAID with acetaminophen were classified as with or without a PPI according to whether or not exposure to the study medication overlapped exposure to a PPI.

GI HOSPITALIZATIONS. In total, 1,854 GI hospitalizations (upper and lower) occurred in study patients during exposure to the study drugs. Among these, 1,432 were in the upper GI tract and 422 in the lower one. Table 2 displays the number of GI hospitalizations by study medication used.

Nonusers of PPIs

OVERALL GI HOSPITALIZATIONS (UPPER AND LOWER). Among patients not using a PPI concurrently with the study drugs, 1,410 overall GI hospitalizations (upper and lower combined) occurred during exposure to study medications. Patients who were using acetaminophen had a similar crude rate of overall GI hospitalizations regardless of acetaminophen dose (≤3 g/day and >3 g/day) (4.3 per 1,000 p-yr and 4.9 per 1,000 p-yr, respectively) (Table 2). These rates seemed higher in those using tNSAIDs (5.1 per 1,000 p-yr) and in those using tNSAIDs concurrently with acetaminophen (8.6 per 1,000 p-yr). The adjusted hazard ratio (HR) of overall GI hospitalization varied only slightly by acetaminophen dose, but it was higher among tNSAID users, 1.63 (95% confidence interval [CI] 1.44–1.85), and among those using a tNSAID concurrently with acetaminophen, 2.55 (95% CI 1.98–3.28), compared with those using acetaminophen ≤3 g/day (Table 3). The combination of a tNSAID and acetaminophen increased the HR of overall GI hospitalizations by 55% compared with tNSAIDs alone, 1.55 (1.20–2.00) (Table 3).

UPPER GI HOSPITALIZATIONS. Of 1,410 overall GI hospitalizations that occurred in nonusers of PPIs, 1,162 (82%) occurred in the upper GI tract (Table 2). The crude rate of upper GI hospitalizations seemed slightly higher in patients using higher doses of acetaminophen (>3 g/day), higher in those using tNSAIDs, and higher in those using tNSAIDs concurrently with acetaminophen compared with those using acetaminophen at lower doses (≤3 g/day) (Table 2). Compared with times on lower doses of acetaminophen, the adjusted HR of upper GI hospitalization was higher during times on higher doses of acetaminophen, 1.23 (1.04–1.46), times on tNSAIDs alone, 1.66 (1.44–1.85), and times on tNSAIDs concurrently with acetaminophen, 2.56 (1.94–3.37) (Table 3). Compared with tNSAID use alone, the HR with the combination of a tNSAID and acetaminophen was 1.53 (1.16–2.03) (Table 3).

Table 1. Patient Characteristics at the Index Date

	PPI Acetaminophen				No PPI Acetaminophen			
	High-Dose	Low-Dose	With tNSAID	tNSAID	High-Dose	Low-Dose	With tNSAID	tNSAID
No. of patients	15,664	39,360	2,002	24,279	84,239	247,608	13,593	217,438
Demographics (%)								
Female	61.9	63.0	58.0	62.4	59.8	60.4	56.7	58.0
Age 66–69 yr	32.2	29.8	37.0	39.0	29.0	28.3	36.8	39.2
Age 70–74 yr	21.1	22.1	24.3	26.9	23.9	24.4	27.9	28.7
Age 75–79 yr	19.6	20.2	20.0	18.6	20.5	20.6	19.3	18.3
Age 80–84 yr	15.0	15.0	11.4	10.2	14.7	14.5	10.0	9.0
Age 85 yr or older	12.1	12.9	7.3	5.3	11.9	12.2	6.1	4.7
Comorbidity indicator (mean ± SD)								
No. of drugs in prior year	8.6 ± 5.8	8.3 ± 5.5	6.7 ± 5.0	6.5 ± 4.9	5.9 ± 4.5	5.7 ± 4.4	4.7 ± 4.0	4.5 ± 3.7
No. of physician billings in prior year	39.2 ± 42.3	36.0 ± 39.3	27.2 ± 32.8	22.5 ± 24.5	23.9 ± 27.2	22.0 ± 25.3	16.2 ± 17.7	14.2 ± 16.0
Musculoskeletal disease (%)								
Osteoarthritis	17.9	16.8	22.4	22.0	15.6	13.7	20.2	18.8
Rheumatoid arthritis	2.8	2.5	4.9	4.8	1.5	1.3	2.2	2.4
Cardiovascular disease (%)								
Congestive heart failure	21.1	19.9	12.2	10.9	14.1	13.0	8.4	7.3
Ischemic heart disease	32.3	30.3	20.9	20.4	21.0	19.4	14.9	13.3
Cerebrovascular disease	9.2	8.2	5.7	4.2	6.5	6.0	3.5	3.0
Antihypertensive agents	50.2	48.5	39.4	39.4	41.2	39.5	32.6	32.3
Antidiabetic agents	17.1	16.2	12.8	11.3	14.2	14.1	12.0	10.6
Comorbid condition (%)								
Renal failure	4.6	4.4	1.8	1.7	2.3	2.3	1.0	0.9
COPD	13.7	12.8	10.9	8.0	9.2	8.7	7.4	5.8
Anemia or blood disease	1.5	1.3	1.0	0.8	0.7	0.7	0.4	0.4
Psychiatric disorders	7.7	7.2	3.4	2.7	6.1	5.4	2.6	2.0
GI events in prior year (%)								
Peptic ulcer disease	4.0	3.9	2.7	2.3	1.0	1.0	0.8	0.7
Visit to gastroenterologist	23.2	23.4	15.3	15.3	8.5	8.2	5.4	4.9
Upper GI diagnostic test	24.3	23.3	15.4	14.8	7.3	7.0	5.1	4.2
Dyspepsia or heartburn	9.0	9.5	5.9	7.2	2.7	2.7	2.2	2.2
Proton pump inhibitor	79.3	81.4	58.9	64.2	8.4	7.8	5.7	11.4
H_2-receptor antagonist	11.1	12.1	12.0	11.7	10.5	10.6	10.0	8.5
Misoprostol	1.0	0.9	2.2	1.8	1.0	0.8	2.5	1.8
Medication known to increase the risk of GI bleeding in prior year								
Aspirin	42.6	40.1	32.9	29.9	32.2	31.0	25.0	22.4
Clopidogrel	5.1	4.0	1.3	1.3	1.5	1.2	0.4	0.3
Anticoagulants	11.6	8.3	4.2	3.3	7.2	8.5	2.5	2.1
Corticosteroids	18.1	17.1	16.6	14.7	10.2	9.3	9.1	8.0

COPD = chronic obstructive pulmonary disease; H_2 = histamine 2.

LOWER GI HOSPITALIZATIONS. Of 1,410 overall GI hospitalizations that occurred in nonusers of PPIs, 248 (18%) were in the lower GI tract (Table 2). Compared with times on lower doses of acetaminophen, the adjusted HR of lower GI hospitalization was higher during times on tNSAID concurrently with acetaminophen, 2.35 (95% CI 1.26–4.37) (Table 3). Compared with tNSAID use alone, the HR with the combination of a tNSAID and acetaminophen was 1.70 (0.90–3.24) (Table 3).

Users of PPIs

OVERALL GI HOSPITALIZATIONS. Among patients using PPIs concurrently with the study drugs, 444 overall GI hospitalizations occurred during exposure to the study drugs. Those who were using acetaminophen also had similar crude rates of overall GI hospitalizations, regardless of acetaminophen dose (≤3 g/day and >3 g/day) (4.2 per 1,000 p-yr and 4.9 per 1,000 p-yr, respectively) (Table 2). This rate seemed lower (3.3 per 1,000 p-yr) in those using tNSAIDs and higher (7.1 per 1,000 p-yr) in those using tNSAIDs concurrently with acetaminophen. The adjusted HR of overall GI hospitalization was similar among those using tNSAIDS or acetaminophen either at the higher (>3 g/day) or lower (≤3 g/day) doses, respectively, compared with the reference category (acetaminophen ≤3 g/day without a PPI). The adjusted HR with the use of the combination of acetaminophen and tNSAIDs was twice as high as that of the reference category (2.15, 95% CI 1.35–3.40). (Table 3). Compared with

Table 2. Prescriptions and Unadjusted Upper and Lower GI Hospitalization Rates in Follow-Up

	Drug Exposure		No. of GI Hospitalizations (Crude Rate/1,000 Patient-Years)		
	No. of Prescriptions	Total Duration (Yr)	Lower	Upper	Lower/Upper
Nonusers of PPIs					
Acetaminophen ≤3 g/day	2,609,232	150,364	130 (0.9)	511 (3.4)	640 (4.3)
Acetaminophen >3 g/day	1,092,891	47,764	43 (0.9)	191 (4.0)	234 (4.9)
Acetaminophen and tNSAIDs	117,914	7,858	11 (1.4)	57 (7.2)	68 (8.6)
tNSAIDs	1,463,323	91,379	64 (0.7)	403 (4.4)	467 (5.1)
PPI users					
Acetaminophen ≤3 g/day	1,032,269	58,344	100 (1.7)	145 (2.5)	245 (4.2)
Acetaminophen >3 g/day	504,943	23,188	40 (1.7)	74 (3.2)	114 (4.9)
Acetaminophen and tNSAIDs	40,800	2,666	7 (2.6)	12 (4.5)	19 (7.1)
tNSAIDs	315,238	19,839	27 (1.4)	39 (2.0)	66 (3.3)

tNSAID = nonselective nonsteroidal anti-inflammatory drug; GI = gastrointestinal.

Table 3. Results of Cox Regression Model With Time-Dependent Exposure to Determine the Association Between Drug Exposure and Upper/Lower GI Hospitalization

	Hazard Ratio (95% CI)		
	Upper/Lower	Upper	Lower
Nonusers of PPIs			
Acetaminophen ≤3 g/day	Referent	Referent	Referent
Acetaminophen >3 g/day	1.20 (1.03–1.40)	1.23 (1.04–1.46)	1.08 (0.76–1.52)
Acetaminophen and tNSAIDs	2.55 (1.98–3.28)	2.56 (1.94–3.37)	2.35 (1.26–4.37)
tNSAIDs	1.63 (1.44–1.85)	1.66 (1.44–1.91)	1.36 (0.99–1.85)
Users of PPIs			
Acetaminophen ≤3 g/day	0.95 (0.81–1.11)	0.73 (0.60–0.89)	1.70 (1.27–2.26)
Acetaminophen >3 g/day	1.16 (0.94–1.43)	0.98 (0.76–1.26)	1.77 (1.22–2.58)
Acetaminophen and tNSAIDs	2.15 (1.35–3.40)	1.68 (0.94–3.00)	4.01 (1.85–8.66)
tNSAIDs	1.07 (0.82–1.39)	0.77 (0.55–1.08)	2.35 (1.52–3.61)
Nonusers of PPIs*			
tNSAIDs	Referent	Referent	Referent
Acetaminophen ≤3 g/day	0.61 (0.54–0.70)	0.60 (0.52–0.70)	0.74 (0.54–1.01)
Acetaminophen >3 g/day	0.73 (0.62–0.86)	0.74 (0.62–0.88)	0.79 (0.53–1.17)
Acetaminophen and tNSAIDs	1.55 (1.20–2.00)	1.53 (1.16–2.03)	1.70 (0.90–3.24)
Users of PPIs			
Acetaminophen ≤3 g/day	0.60 (0.48–0.69)	0.44(0.35–0.54)	1.23 (0.86–1.76)
Acetaminophen >3 g/day	0.70 (0.56–0.87)	0.58 (0.44–0.76)	1.27 (0.82–1.97)
Acetaminophen and tNSAIDs	1.29 (0.81–2.06)	1.00 (0.56–1.79)	2.88 (1.30–6.37)
tNSAIDs	0.65 (0.50–0.85)	0.46 (0.33–0.65)	1.71 (1.08–2.73)
Time-dependent variables assessed at the filling date of each prescription			
Concomitant aspirin	1.76 (1.59–1.95)	1.70 (1.52–1.91)	1.98 (1.60–2.43)
Concomitant clopidogrel	1.67 (1.29–2.16)	1.47 (1.07–2.03)	2.21 (1.43–3.41)
Concomitant anticoagulants	1.98 (1.68–2.33)	1.71 (1.41–2.09)	2.86 (2.13–3.83)
Female	0.71 (0.65–0.79)	0.71 (0.64–0.79)	0.73 (0.59–0.89)
Age at the index date (for every 5-yr increase)	1.26 (1.22–1.30)	1.22 (1.18–1.27)	1.38 (1.28–1.47)
Variables assessed based on 1-yr data prior to index date			
Number of physician billings (increase by 10)	1.05 (1.03–1.06)	1.04 (1.02–1.06)	1.06 (1.04–1.09)
Alcohol or drug abuse	1.80 (1.17–2.77)	1.92 (1.19–3.10)	1.46 (0.54–3.91)
Diagnosis with peptic ulcer disease	1.84 (1.45–2.32)	1.78 (1.34–2.37)	1.96 (1.29–2.96)
Visited a gastroenterologist	1.33 (1.14–1.56)	1.18 (0.98–1.43)	1.78 (1.34–2.35)
PPI utilization	0.80 (0.70–0.93)	0.81 (0.68–0.97)	0.77 (0.59–1.01)
Misoprostol/H_2RA utilization	1.15 (1.03–1.28)	1.16 (1.02–1.32)	1.10 (0.88–1.38)
Corticosteroids utilization	1.15 (1.01–1.32)	1.02 (0.86–1.20)	1.61 (1.25–2.06)
Diagnosis with osteoarthritis	0.85 (0.76–0.95)	0.82 (0.71–0.93)	0.96 (0.78–1.20)

*Same model as above with tNSAIDs as a reference group.

tNSAID use alone, the HR with the combination of a tNSAID and acetaminophen was 1.29 (0.8–2.06) (Table 3).

UPPER GI HOSPITALIZATIONS. Of the 444 overall GI hospitalizations that occurred in users of PPIs, 270 (61%) occurred in the upper GI tract (Table 2). The crude rate of upper GI hospitalizations seemed slightly higher in patients using higher doses of acetaminophen (>3 g/day) and higher in those using tNSAIDs concurrently with acetaminophen compared with those using acetaminophen at lower doses (≤3 g/day) (Table 2). Compared with times on lower doses of acetaminophen without a PPI, the adjusted HR of upper GI hospitalization was higher during times on either lower doses of acetaminophen and a PPI, 1.70 (1.27–2.26), or higher doses of acetaminophen and a PPI, 1.77 (1.22–2.58); times on a tNSAIDs alone, 2.35 (1.52–3.61); and times on a tNSAID concurrently with acetaminophen, 4.01 (1.85–8.66) (Table 3). Compared with tNSAID use alone, the HR with the combination of a tNSAID and acetaminophen was 1.00 (0.56–1.79) (Table 3).

LOWER GI HOSPITALIZATIONS. Of the 444 overall GI hospitalizations that occurred in nonusers of PPIs, 174 (39%) were in the lower GI tract (Table 2). Compared with times on lower doses of acetaminophen without a PPI (reference category), the adjusted HRs of lower GI hospitalization were higher in all groups (Table 3). Compared with tNSAID use alone, the HR with the combination of a tNSAID and acetaminophen was 2.88 (1.30–6.37) (Table 3).

Risk Factors for Overall GI Hospitalizations

The Cox regression model also revealed that women were at a lower risk of GI hospitalizations than men (HR 0.71, 95% CI 0.65–0.79). Concomitant use of prescription aspirin increased the risk of GI hospitalizations (HR 1.76, 95% CI 1.59–1.95), as did concomitant use of an anticoagulant (HR 1.98, 95% CI 1.68–2.33) or clopidogrel (HR 1.67, 95% CI 1.29–2.16). Older age, a diagnosis of alcohol or drug abuse in the prior year, a diagnosis of peptic ulcer in the prior year, and a visit to a gastroenterologist in the prior year were also associated with an increased risk of GI hospitalization (Table 3).

Subgroup Analyses

In total, 393,510 patients (61% of the total cohort) had not received any NSAID (including COX-2 inhibitors and meloxicam) or acetaminophen medication in the year prior to the index date. Among these new users, 637 patients were hospitalized for a GI event in follow-up, 508 (79.7%) for events occurring in the upper GI tract. Cox regression model results for this subgroup did not differ meaningfully from the results obtained for the complete cohort. The results did not change either when we restricted the analyses to patients who did not have any GI event in the year prior to the index date. The results also did not change when we included only new patients who did not have any GI event in the prior year (data not shown).

Analyses restricted to those with prior OA or RA diagnoses (115,305 patients, 18% of the cohort) resulted in estimates similar to those obtained for the complete cohort. In this subgroup, 456 patients were hospitalized for GI events during follow-up, 340 (74.6%) for events occurring in the upper GI tract. The adjusted HRs of GI hospitalization for this subgroup were generally similar to those of the complete cohort, but the risk of GI events with the use of acetaminophen >3 g/day was slightly higher than that of the main cohort (HR 1.42, 95% CI 1.04–1.93); this was mainly due to a higher risk of upper GI events among this subgroup (HR 1.51, 95% CI 1.07–2.13).

Sensitivity Analyses

The effects of varying definitions of exposure and outcome in the four sensitivity analyses are shown in Table 4. As for the base-case scenario, HRs of GI hospitalization were adjusted for baseline patient characteristics and concomitant use of prescription aspirin, anticoagulants, clopidogrel, and

Table 4. Sensitivity Analyses Using Cox Regression Models Adjusted for Patient Characteristics at the Index Date to Determine the Association Between Drug Exposure and Upper/Lower GI Hospitalization

		Sensitivity Analysis			
Drug Exposure Category	Primary Analysis	1	2	3	4
Nonusers of PPIs					
Acetaminophen ≤3 g/day	Referent	Referent	Referent	Referent	Referent
Acetaminophen >3 g/day	1.20 (1.03–1.40)	0.86 (0.71–1.03)	1.26 (1.05–1.51)	1.21 (1.05–1.39)	1.26 (1.08–1.48)
Acetaminophen and tNSAIDs	2.55 (1.98–3.28)	2.23 (1.75–2.83)	2.36 (1.32–4.22)	2.49 (1.95–3.19)	2.67 (2.06–3.47)
tNSAIDs	1.63 (1.44–1.85)	1.42 (1.26–1.60)	1.40 (1.19–1.63)	1.60 (1.41–1.80)	1.60 (1.40–1.84)
Users of PPIs					
Acetaminophen ≤3 g/day	0.95 (0.81–1.11)	0.84 (0.72–0.96)	0.98 (0.81–1.19)	0.93 (0.80–1.09)	1.00 (0.84–1.18)
Acetaminophen >3 g/day	1.16 (0.94–1.43)	1.08 (0.84–1.39)	1.28 (0.98–1.65)	1.13 (0.92– 1.38)	1.24 (0.99–1.54)
Acetaminophen and tNSAIDs	2.15 (1.35–3.40)	2.11 (1.42–3.13)	2.09 (0.52–8.41)	2.15 (1.37–3.37)	2.16 (1.33–3.52)
tNSAIDs	1.07 (0.82–1.39)	1.09 (0.87–1.36)	0.93 (0.63–1.35)	1.13 (0.88–1.44)	1.10 (0.84–1.45)

1. First sensitivity analysis: event attributed to drug switched from for all switchers.
2. Second sensitivity analysis: follow-up terminated at first switch.
3. Third sensitivity analysis: events that occurred during 150% of number of supplied days are attributed to the supplied drug.
4. Fourth sensitivity analysis: only events that occurred during the supplied days are attributed to the supplied drug.

Table 5. Number of Prescriptions From Each Study Medication in the 3 Months Following the Withdrawal of Rofecoxib (October 2004 to December 2004) and During Similar Periods of 2002 and 2003

	Number of Prescriptions Dispensed Between October 1 and December 31		
	2002	2003	2004
Acetaminophen (≤3 g/day)	90,292	91,282	90,860
Acetaminophen (>3 g/day)	40,961	43,276	45,609
Acetaminophen (≤3 g/day) with a PPI	48,762	55,665	61,057
Acetaminophen (>3 g/day) with a PPI	24,209	28,612	32,803
tNSAIDs	29,350	27,605	33,923
tNSAIDs with a PPI	11,072	11,107	17,300
Both tNSAIDs and acetaminophen	2,239	2,141	2,865
Both tNSAIDs and acetaminophen with a PPI	1,439	1,477	2,123

corticosteroids in follow-up. Results of all sensitivity analyses were similar to those of the base-case scenario except that the HR of GI hospitalization during exposure to acetaminophen >3 g/day in sensitivity analysis 1 was lower than in the base-case scenario and in the other sensitivity analyses. The rules applied in sensitivity analysis 1 increased the rate of GI hospitalizations with acetaminophen ≤3 g/day from 4.3 per 1,000 p-yr in the primary analysis to 4.7 per 1,000 p-yr, while the rate with acetaminophen >3 g/day decreased from 4.9 per 1,000 p-yr to 3.9 per 1,000 p-yr. This suggests that more patients switched from the lower doses of acetaminophen before the end of their medication supply than those from the higher doses of acetaminophen.

Additional Analyses

While the utilization of acetaminophen ≤3 g/day without a PPI remained stable between the periods October 2002 and December 2002 and October 2004 and December 2004, an increase was observed in the utilization of all other exposure categories, for example, the number of prescriptions for tNSAIDs with concomitant PPIs increased by 56% over this time period and those for both tNSAIDs and acetaminophen increased by 28% (Table 5).

DISCUSSION

Our findings indicate that among elderly patients in need of analgesic therapy, the use of tNSAIDs in combination with acetaminophen may be associated with a more than 50% increased risk of GI hospitalization compared with the use of tNSAIDs alone. Although the use of PPIs appeared to mitigate this risk somewhat, among PPI users the GI risk with the combination was still higher than that with the other therapies considered in this study. These results suggest that tNSAIDs in combination with acetaminophen should be avoided; however, this cannot be concluded definitively because the combination of acetaminophen with tNSAIDs may be indicated for patients with a high level of pain such that they would otherwise be prescribed a high dose of one NSAID or more than one NSAID concomitantly. Our study did not compare the risk of GI bleeding associated with the combination of acetaminophen with tNSAIDs *versus* these alternative choices.

The increased risk of GI hospitalizations observed in our study during the concomitant use of tNSAIDs and acetaminophen may be explained, in part, by the additional inhibition of the COX enzyme induced by acetaminophen (27). tNSAIDs inhibit the two COX isoforms, COX-1 and COX-2, to various extents (27). It is believed that inhibition of COX-2 is responsible for the anti-inflammatory and analgesic effects of tNSAIDs and that inhibition of COX-1 causes the GI adverse events (28). *Ex vivo* studies have shown that acetaminophen is a weak, reversible, nonspecific COX inhibitor (27, 29). In rats in which inflammatory conditions and gastric acidity were induced, gastric mucosal injury was observed with exposure to acetaminophen but not in the absence of such exposure (30).

Similar to previous studies, our study found that the rate of tNSAID-related hospitalizations for upper GI events was higher than that for lower GI events (13). Clinical practice guidelines recommend the use of a GPA with tNSAIDs in elderly patients to reduce the risk of upper GI bleeding. The effect of a GPA in reducing the risk of NSAID-related lower GI lesions is not clear, but our findings indicate that PPIs may not protect against lower GI hospitalization. Indeed, in this study, patients who were using a PPI with the study medications had slightly higher adjusted rates of hospitalizations for lower GI events than those who were not using a PPI (compared with the common referent group of acetaminophen <3 g/day).

Few prior studies have assessed the risk of lower GI bleeding associated with tNSAIDs (13–18) and none have examined the risk of either upper or lower GI bleeding associated with the combination of tNSAID with acetaminophen. A recent systematic review reported that the risk of a tNSAID-related lower GI adverse effects varied among studies and ranged from about 2- to 18-fold higher than that of patients not using these medications (31). The review did not examine the risk of NSAID-related lower GI adverse events among patients using PPIs.

Our results also indicate that the risk of GI hospitalization was higher when patients were using acetaminophen at doses higher than 3 g per day. Although these results are consistent with those of a recent review that found that acetaminophen at doses higher than 2 g per day was associated with a significant 3.6-fold increase of upper GI complications compared with nonuse (8), the increase in our study was small (20%) and should be interpreted with caution because of a possible residual selection bias occurring if, for example, patients with greater pain and a higher risk of GI bleeding were prescribed higher doses of acetaminophen rather than lower doses. Although our model adjusted for all GI risk factors that are recorded in the database, information on the history of GI risk factors may have been incomplete or inaccurate. We should also note that our sensitivity analyses indicated that many of the events observed during exposure to higher doses of acetaminophen were in patients who had switched to acetaminophen or increased the dose, which may explain

at least some of the increase in the risk observed with higher doses of acetaminophen. Use of a PPI with high doses of acetaminophen seemed to protect against upper GI events but not against lower GI events. However, we cannot exclude the possibility that PPI users were at a higher risk of lower GI events because of the reasons for which the PPI was prescribed. Indeed, many patients with GI symptoms are prescribed a PPI without undergoing further GI investigations. Some of these symptoms may be caused by an ulcer in the small bowel or lower GI tract, and a PPI may not be helpful for these (31). To verify this hypothesis, we compared lower GI hospitalizations in PPI users *versus* nonusers for all study drugs respectively. The risk in PPI users was higher by 61–71% for all study drugs (data not shown).

These findings and the need to use a PPI with high doses of acetaminophen should be confirmed in other independent studies.

The strength of our study design includes the use of large, population-based administrative databases that contained data collected independently of the study objectives, which afforded us the opportunity to examine the risk of GI hospitalization associated with tNSAIDs and acetaminophen use in the clinical practice setting. The databases included a large number, but not all, of the relevant variables for the study questions. The database also allowed for assessment of outcomes over an extended follow-up period.

Limitations of the study also pertain to the use of administrative databases in which the indication for which a medication is prescribed and actual drug consumption are not known. For example, compliance with the prescription regimen and indications for which the PPI was prescribed could not be assessed. Also the presence of *Helicobacter pylori* (*H. pylori*) is not available in the database and could not be assessed. However, treatment with HP-Pac was considered as a proxy for the presence of *H. pylori*. Treatment with HP-Pac was first entered in the multivariable model, but was not kept after we applied the variable selection criteria. Also, information on a history of GI bleeding and other potential risk factors for GI hospitalizations may be incomplete in the physician billing database. However, for some variables, such as a history of GI bleeding, we also used the prescription claims database to assess prior GPA use and the physician billing database to assess the type of GI procedure performed. GPA use in the year prior to the index date is a good proxy for the presence of an ulcer or ulcer symptoms in that year, and the RAMQ prescription claims database has been validated and found to be both accurate and reliable (32). Our study considered tNSAIDs as a class and did not adjust for multiple NSAID use, medication dosages, and chronic *versus* intermittent medication use. Although it will be interesting to study the occurrence of GI hospitalization in association with these risk factors, we did not choose to do so in this study because it would have complicated substantially the analyses. Our analyses provide a global assessment of the upper and lower GI risk overall utilization regimens of the study drugs.

Information on over-the-counter use of ibuprofen, aspirin, acetaminophen, and GPA was not available. With respect to the latter problem, a recently published study found that over-the-counter use of ibuprofen at lower than prescribed doses was relatively safe from a GI point of view, while use at higher doses (similar to prescription levels) was associated with serious GI toxicity (33). Based on a communication with the Institut de la Statistique du Québec/Direction Santé Québec, a government agency, 46.3%, 17.0%, 2.2%, and 1.1% of the elderly who consumed acetaminophen, tNSAIDs, aspirin, and GPAs, respectively, in 1998 acquired them over the counter. However, because patients were included in this study cohort only if they had a prescription for a tNSAID or acetaminophen and were examined only during times of active prescriptions of these medications, they may have been less likely to also use over-the-counter acetaminophen or tNSAIDs during these times. As in other population-based observational studies of tNSAID use in Canada (34), patients had strong financial incentives to obtain their medications via prescription rather than by over-the-counter purchase, which is not reimbursed by the provincial drug plan. Nevertheless, although we attempted to control for all risk factors for NSAID-related GI hospitalizations, residual bias or confounding may still have been present. The magnitudes of risk estimates in some of the exposure categories in this study are such that they could not have resulted from these problems.

In conclusion, our study found that, in an elderly population, the risk of GI hospitalization might be higher when using tNSAIDs and acetaminophen in combination. Our study also found that the coprescription of a PPI with tNSAIDs might protect against upper, but not lower, GI events. Further research of this topic is needed to better characterize the upper and lower GI risks associated with various analgesic treatment options for elderly patients, especially those in need of chronic therapy.

STUDY HIGHLIGHTS

What Is Current Knowledge

- Traditional NSAIDs increase the risk of upper GI adverse events.
- Co-prescription of a PPI with traditional NSAIDs protects against NSAID-related upper GI adverse events.
- Acetaminophen is GI-safer than traditional NSAIDs.

What Is New Here

- Combination of traditional NSAIDs with acetaminophen increases the risk of upper GI events beyond that of traditional NSAIDs alone.
- Co-prescription of PPI with the combination NSAID and acetaminophen may protect against upper GI adverse events.

- Co-prescription of PPI with the combination NSAID and acetaminophen does not protect against lower GI adverse events.

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Received June 8, 2007; Accepted November 20, 2007.

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CONFLICT OF INTEREST

Guarantor of the article: Elham Rahme, Ph.D.

Specific author contributions: Elham Rahme participated in the design of the study, data acquisition, supervision of data analyses, and writing the first draft of the manuscript. Alan Barkun participated in the design of the study, the definition and identification of the outcomes, interpretation of the results, and critical appraisal of the manuscript. Douglas Watson participated in the design of the study and critical appraisal of the manuscript. Sabine Gaugris participated in the critical appraisal of the manuscript. Hacene Nedjar conducted the data analyses.

Financial support: The study is supported by a grant from Merck & Co., Inc. In addition, Alan Barkun and Elham Rahme obtained consultancy fees from the company. Elham Rahme is a research scholar funded by the Fonds de la Recherche en Santé du Quebec (FRSQ). Alan Barkun is a recipient of a FRSQ-National Clinical Investigator Award.

Potential competing interests: Douglas Watson and Sabine Gaugris are employees of Merck & Co., Inc. Elham Rahme has received grant support and consultancy fees from Merck & Co., Inc., Pfizer, Inc., Boehringer Ingelheim, and Chiesi Farmaceutici. Alan Barkun has received consultancy fees from Merck & Co., Inc., and Astra Zeneca Canada, Inc. Sabine Gaugris and Douglas J. Watson are currently employed by Merck & Co., Inc. Hacene Nedjar has no conflict of interest to declare.