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Increase in Nonfatal Digestive Perforations and Haemorrhages Following Introduction of Selective NSAIDs

A Public Health Concern

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Abstract

Background and objective: This article documents the impact of the introduction of selective NSAIDs on overall prescription patterns of NSAIDs and associated gastroprotective agents (GPAs), and on the rate of nonfatal digestive perforations and haemorrhages.

Methods: A retrospective, closed cohort study was conducted using the Quebec Health Insurance Board databases, for a 3-year period overlapping the introduction of selective NSAIDs. All adult subjects who were continuously registered with the Public Prescription Drug Program (PPDP) between 1 January 1999 and 31 December 2001 (n = 2 052 231) were included. Prescriptions for NSAIDs (selective [celecoxib, rofecoxib and meloxicam] and nonselective), concomitant use of GPAs and nonfatal digestive perforations or haemorrhages diagnosed in hospital were compiled. Data were analysed on an annual basis according to age, sex and patient risk of gastrointestinal (GI) complications.

Results: The listing of selective NSAIDs in the PPDP formulary was followed by a 28.2% increase in the prevalence of NSAID use from 19.5% in 1999 to 25% in 2001. The proportion of long-term users also evolved rapidly with a 135% increase over 3 years. From 1999 to 2001, there was a 75.9% increase in the rate of nonfatal digestive perforations and haemorrhages in the presence of NSAIDs.

Conclusion: The introduction of selective NSAIDs stimulated NSAID use and coincided with an increased incidence of nonfatal digestive perforations and haemorrhages in the presence of NSAIDs. Selective NSAIDs should be prescribed with caution to persons at risk for GI complications.

Background

NSAIDs are among the most widely prescribed drugs for the treatment of inflammatory conditions, including arthritis and pain.[1] They act by inhibiting cyclo-oxygenase (COX), a key enzyme in the cascade leading to inflammation.[2] However, inactivation of the COX-1 enzyme in gastric tissues decreases the production of prostaglandins that protect the gastric mucosa,[3] inducing ulcer formation, per-

foration and bleeding that can be fatal.[4] Selective NSAIDs were specifically developed to reduce NSAID gastrointestinal (GI) toxicity by sparing COX-1 activity while inhibiting COX-2, which produces the inflammatory response.[2,3]

Selective and nonselective NSAIDs have shown similar efficacy in controlling symptoms of inflammation but because of higher acquisition costs of the former, guidelines recommend prescription of selective NSAIDs only for patients at risk for GI complications.[4-7] Indeed, their GI safety compared with nonselective NSAIDs has been shown in prospective clinical trials.[8-11] However, the results of some clinical trials were questioned in follow-up studies.[12] In addition, one retrospective observational study reported an increased incidence of GI events associated with increased use of selective NSAIDs in elderly patients, which sparked controversy on the impact of selective NSAIDs from a population perspective.[13] NSAID-prescription patterns suggest that guidelines are not followed, leading to overprescription of the selective NSAIDs.[11,14]

The objectives of this study were to document changes in the prescription patterns of all NSAIDs and gastroprotective agents (GPAs) and in the rate of nonfatal digestive perforations and haemorrhages in current NSAID users following the introduction of selective NSAIDs.

Methods

Study Design, Subjects and Data Collection

A retrospective closed cohort study was performed to assess NSAID use and nonfatal digestive perforations and haemorrhages occurring in the presence or absence of NSAIDs in subjects aged ≥18 years who were continuously registered with the Quebec Public Prescription Drug Program (PPDP) between 1 January 1999 and 31 December 2001. PPDP covers ambulatory drug use for residents aged ≥65 years, welfare recipients and individuals who do not have access to a collective private drug plan, which represented 43% of the Quebec population in 1999.[15]

Individuals were assigned to static age groups according to their age at study entry. Data were collected from three administrative databases managed by the Quebec Health Insurance Board – the Régie de l'assurance maladie du Québec (RAMQ). These were (i) pharmacist reimbursement requests (drug code, prescription dispensing date and duration, and quantity of dispensed drug); (ii) physician payment requests (procedures and diagnoses); and (iii) individual files from RAMQ-insured persons. The pharmacist reimbursement requests database has been described in more detail elsewhere.[16]

NSAID Prescription and Use

Prescriptions for all NSAIDs listed in the Quebec formulary were retrieved. Selective NSAIDs included in the study were celecoxib (listed on the formulary 1 October 1999), rofecoxib (listed on the formulary 1 April 2000) and meloxicam (listed in formulary 1 January 2001). In 2001, meloxicam accounted for 2.8% of selective NSAID prescriptions. Nonselective NSAIDs included in the study were aspirin (acetylsalicylic acid) at dosages of >2.4 g/day, diclofenac, diclofenac potassium, diclofenac/misoprostol, diflunisal, etodolac, fenoprofen, ibuprofen, indometacin, ketoprofen, mefenamic acid, nabumetone, naproxen, phenylbutazone, piroxicam, salsalate, sulindac, tiaprofenic acid, tolmetin sodium and tenoxicam.

The prevalence of NSAID use was assessed on an annual basis, according to the type of NSAID used (selective, nonselective or both) and treatment duration (short- or long-term). Short-term users received NSAID treatment of ≤30 days within a period not exceeding 30 consecutive days and did not receive any NSAID prescription in the 180 days preceding or following the NSAID treatment. Long-term users received NSAID treatment for ≥180 days during a given study year. Any user falling outside of these definitions was recorded as 'other'.

NSAID and Gastroprotective Agent Prescription Patterns

Based on the first NSAID prescription acquired in each study year, NSAID users were stratified

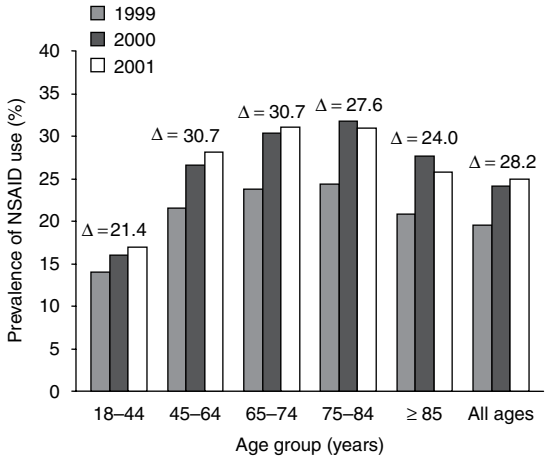

Fig. 1. Prevalence of NSAID use in insured persons by age group from 1999 to 2001. Δ = the percentage change in prevalence of NSAID use between 1999 and 2001.

according to risk status for GI complications, type of NSAID and concomitant GPA (including proton pump inhibitors [PPIs], histamine H_2 receptor antagonists and misoprostol) use. Risk status was established based on five recognised risk factors:[6,17] (i) history of investigated gastroduodenal ulcer or digestive perforations or haemorrhages in hospitalised and ambulatory patients; (ii) age ≥75 years on 1 January of study year; (iii) concomitant use of oral corticosteroids; (iv) concomitant use of anticoagulants; and (v) concomitant use of low-dose aspirin (≤325mg) in the 60–74 year olds. Concomitant use of corticosteroids, anticoagulants, low-dose aspirin and GPAs was defined as dispensation on the same date as the first NSAID dispensing date or dispensation prior to the NSAID dispensing date but with prescription duration extending at least to the NSAID dispensing date. History of gastroduodenal ulcers (subdivisions 3, 7, 9 of the International Classification of Diseases – 9th Edition [ICD-9] codes 531, 532, 533 and 534) was searched in the preceding year and history of digestive perforations and haemorrhages (subdivisions 0, 1, 2, 4, 5, 6 of ICD-9 codes 531, 532, 534 and subdivisions 0, 1, 9 of ICD-9 code 578) was searched going back to 1996.

Nonfatal Digestive Perforations or Haemorrhages in the Presence of NSAIDs

Diagnoses of nonfatal digestive perforations or haemorrhages made in hospitals were retrieved for the study cohort. Nonfatal perforations and haemorrhages were considered to occur in the presence of NSAIDs if NSAID use lasted until the event or ended in the 30 days before the event based on the prescription duration. In such cases, risk status and concomitant drug use were established 30 days before the event. The age of patients was updated for each study year.

Results

Study Population

The closed cohort comprised 2 052 231 persons, of which a majority were women (56.2%). The elderly (≥65 years of age) formed 34.7% of the study population, including 1.9% aged ≥85 years. The largest age group, which comprised the 18–44 year olds, represented 36.9% of the cohort.

Trends in NSAID Use

From 1999 to 2001, the prevalence of NSAID use increased in all age groups (figure 1). The launch of selective NSAIDs was followed by a 28.2% increase in the overall prevalence of NSAID use, going from 19.5% in 1999 to 25.0% in 2001. This trend was consistent for all age groups and, with no marked differences in magnitude, ranged from 21.4% (18–44 years) to 30.7% (45–74 years). The prevalence of NSAID use also increased with age up to the 65–84 years groups. In 2001, 30.8% of the elderly (≥65 years) received at least one NSAID prescription compared with 21.9% in the 18–64 age groups.

Prescriptions for selective NSAIDs rapidly outnumbered those for nonselective NSAIDs (figure 2a). The proportion of NSAID users who received at least one selective NSAID prescription increased from 36.8% in 1999 to 78.5% in 2001. The proportion of long-term users to all NSAID users also evolved rapidly, from 6.9% (27 606) in 1999 to

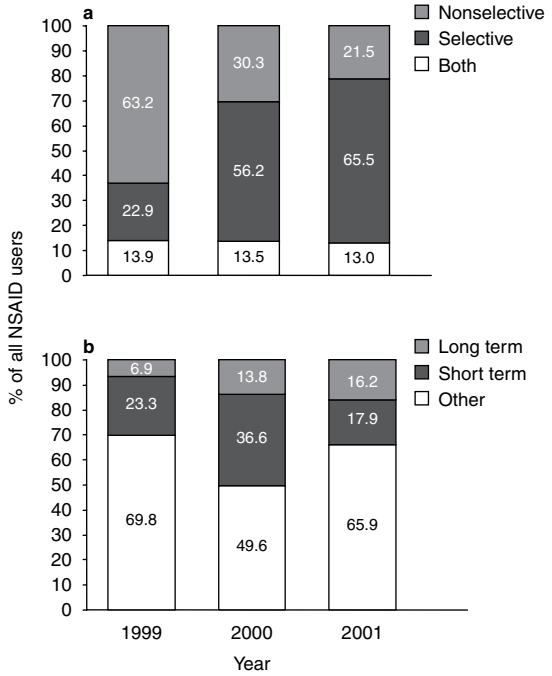

Fig. 2. (**a**) Type of NSAID used and (**b**) duration of NSAID treatment from 1999 to 2001 (NSAID stratification based on NSAIDs used during the year).

16.2% (82 859) in 2001 (figure 2b). These proportions varied with age, from 1.8% in 1999 to 4.6% in 2001 for the youngest group (18–44 years), from 9.8% to 22.6% for the elderly (65–84 years) and from 12.2% to 27.3% for the very elderly (≥85 years).

Risk Factors and Prescribing Patterns

In 2001, 67.5% of users not at risk for GI complications received selective NSAIDs, including 78.3% of long-term users and 56.1% of short-term users (figure 3). Among selective NSAID users, 15.2% were also prescribed a GPA compared with 17.9% in users of nonselective NSAIDs. In users with at least one risk factor, 82.0% received a selective NSAID (figure 3), including 83.5% of long-term users and 78.3% of short-term users. Of those who were prescribed nonselective NSAIDs, 37.5% received a GPA. A higher proportion of long-term users received a GPA compared with short-term users (31.9% vs 12.1%, respectively). The proportion of selective NSAID users increased with the number of risk factors, going from 83% in long-term users with a single risk factor to 100% of users with more than three risk factors. In 2001, PPIs represented 81% of GPA prescriptions, H_2 receptor antagonists 16% and misoprostol 3%. Long-term users at risk for GI complications increased from 35.9% in 1999 to 44.3% in 2001. In this group, the percentage of users aged ≥75 years increased from 24.4% to 30.9%.

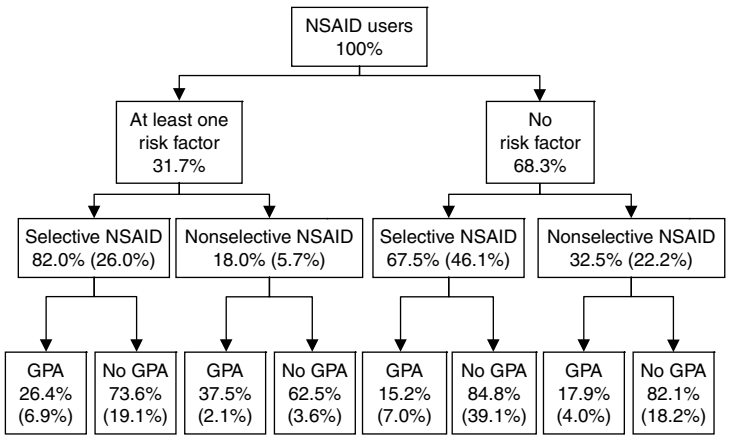

Fig. 3. Proportion of NSAID users in the Québec Public Prescription Drug Program cohort by risk factor, type of NSAID used and gastroprotective agent (GPA) cotherapy in 2001 (NSAID stratification based on the first prescription of the year; numbers in parentheses indicate the absolute proportion of all NSAID users).

Rates of Nonfatal Digestive Perforations and Haemorrhages

Rates of nonfatal digestive perforations and haemorrhages per 10 000 insured persons in the study cohort are shown in table I. The rate of nonfatal perforations and haemorrhages increased by 13.3%: from 3.68 in 1999 to 4.17 in 2001. Rates of perforations and haemorrhages occurring in the absence of NSAIDs remained relatively constant with a 2.5% increase over 3 years from 3.14 to 3.22, whereas perforations and haemorrhages in the presence of NSAIDs rose by 75.9% from 0.54 to 0.95. This augmentation was attributable to perforations and haemorrhages in the presence of selective NSAIDs, which increased by 1340.0% from 0.05 to 0.72, whereas perforations and haemorrhages in the presence of nonselective NSAIDs followed an opposite trend, with a 53.1% decrease from 0.49 to 0.23.

The majority of nonfatal digestive perforations and haemorrhages occurred during the course of NSAID treatment (57%), a proportion rising to 90% when perforations and haemorrhages that occurred within a 15-day period following the end of treatment were included. When analyses were restricted to only perforations and haemorrhages that occurred during the course of NSAID treatment, the rates increased by 1486% for selective NSAIDs (from 0.03 to 0.46) and decreased by 65% for nonselective NSAIDs (from 0.26 to 0.09).

The incidence of nonfatal perforations and haemorrhages in the presence of NSAIDs increased markedly with age (figure 4); however, the upward trend was observed for all age groups. Increases ranged from 14.3% in the 18–44 years age group to 210.3% in the very elderly (≥85 years). Overall, the proportion of users who were considered at risk for GI complications and who experienced a nonfatal digestive perforation or haemorrhage increased from 56.0% in 1999 to 74.9% in 2001 (table II). The evolution of the rates of digestive perforations and haemorrhages in the presence of NSAIDs over the 3-year study period were broken down among the five risk factors (table II). Except for the concomitant use of aspirin (≤325 mg/day), there was a notable increase in the rates of digestive perforations and haemorrhages for every risk factor ranging from 43.3% for being aged ≥75 years to 244.4% for concomitant use of anticoagulants. In 2001, 83.1% of nonfatal digestive perforations and haemorrhages occurred in users receiving either a selective NSAID (75.9%, including 23.6% also receiving a GPA) or a nonselective NSAID with a GPA (7.2%). The proportion of patients of all ages with perforations and haemorrhages in the presence of NSAIDs with the concomitant use of aspirin increased from 29.4% in 1999 to 35.4% in 2001; for the persons with perforations and haemorrhages in the absence of NSAIDs, the percentages rose from 15.1% to 25.0%. In comparison, these percentages among overall NSAID users went from 6.4% to 13.4%.

Discussion

A marked increase in NSAID use was observed in persons registered with the Québec PPDP after the introduction of selective NSAIDs, which was attributable to the rapid uptake of these products. Similar increases were observed worldwide.[13,14] Because GI toxicity was the main factor limiting the use of nonselective NSAIDs,[5] both improved GI-safety claims with selective NSAIDs and their indication for individuals at risk for GI complications

Table I. Rate of nonfatal digestive perforations or haemorrhages (NFDP&Hs) in the presence or absence of NSAIDs per 10 000 insured persons

NFDP&Hs	1999	2000	2001	2001/1999 (%)
In insured persons	3.68	4.00	4.17	+13.3
In the absence of NSAID use	3.14	3.18	3.22	+2.5
In the presence of NSAIDs	0.54	0.82	0.95	+75.9
nonselective NSAIDs	0.49	0.29	0.23	−53.1
selective NSAIDs	0.05	0.53	0.72	+1340.0

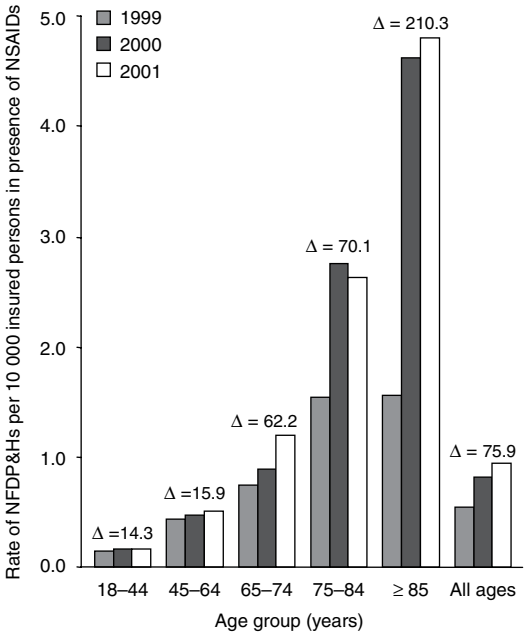

Fig. 4. Rate of nonfatal digestive perforations and haemorrhages (NFDP&Hs) per 10 000 insured persons in the presence of NSAIDs by age group from 1999 to 2001. Δ = the percentage change in prevalence of NSAID use between 1999 and 2001.

contributed to a rapid increase in their use, particularly by the elderly and other persons at risk.

The increase in selective NSAID prescriptions was paralleled by a substantial increase in the relative numbers of nonfatal digestive perforations and haemorrhages. It should be noted that rates of digestive perforations and haemorrhages occurring in the presence of NSAIDs were not reported on the number of NSAID users but rather on the total insured population. Therefore, changes in the rates of perforations and haemorrhages reported for selective or nonselective NSAIDs are linked with the prevalence of their respective use, given that the denominator (per 10 000 insured persons) was the same throughout the study. For that reason, increases or decreases in nonfatal digestive perforation and haemorrhage rates in the presence of either type of NSAIDs must be interpreted in light of changes in the prevalence of their respective use. The striking increase of 75.9% in the rate of perforations and haemorrhages in the presence of NSAIDs can be explained not only by increased population exposure to NSAIDs but also by an important increase of the proportion of both long-term users and users at risk for GI complications. Indeed, the number of long-term NSAID users tripled over the study period. In addition, for the year 2001, >50% of digestive perforations and haemorrhages in the presence of NSAIDs occurred in persons ≥75 years and 75% in persons with at least one risk factor.

Although a causal link between selective NSAID use and nonfatal digestive perforations and haemorrhages cannot be established from the data reported here, the temporal correlation and biological mechanism underlying the pathogenesis of ulcers in the presence of NSAIDs strongly suggest that they are related. It has been proposed that COX-2-derived prostaglandins accelerate ulcer healing through various growth factors including hepatocyte growth factor and gastrin,[18] which raises questions about the long-term GI safety of selective NSAIDs. Recent evidence from a clinical trial involving patients with a history of GI complications suggested that selective NSAIDs failed to provide adequate gastroprotection in this category of patients.[19] Other studies reported no GI-safety benefits with selective NSAIDs in the presence of low-dose aspirin.[10,11]

The five risk factors considered in this study probably did not capture all patients at risk for GI complications. Other risk factors may be invoked, such as concomitant use of selective serotonin reuptake inhibitors[20] or the simultaneous presence of at least two factors, such as high-dose NSAID

Table II. Proportion of patients with nonfatal digestive perforations or haemorrhages (NFDP&Hs) in the presence of NSAIDs and risk factors for gastrointestinal complications

Risk factor	1999 (%)	2000 (%)	2001 (%)
History of investigated gastroduodenal ulcer or NFDP&Hs	8.3	17.9	14.9
Concomitant use of corticosteroids	4.6	4.2	11.3
Concomitant use of anticoagulants	1.8	7.7	0.2
Aged ≥75 years	35.8	53.0	51.3
Concomitant use of aspirin (acetylsalicylic acid) ≤325 mg/day in patients aged 60–74 years	13.8	11.9	13.3
At least one of the above risk factors	56.0	74.4	74.9
Number of NFDP&Hs in the presence of NSAIDS	109	168	195

use, concomitant use of several NSAIDs or a history of cardiovascular disease that can also contribute to the development of GI complications.[6,21] On the other hand, the number of patients with a history of GI complications may be overestimated by an erroneous diagnosis of GI ulcer.

The use of a closed cohort has two main limitations. Patients who had a fatal digestive perforation or haemorrhage as well as those who had a nonfatal digestive perforation or haemorrhage but who died from any other cause before 31 December 2001 were not included in the study population. This implies that the rate of digestive perforation and haemorrhage is underestimated in the current analysis. Another source of bias is attributable to aging of the cohort throughout the study period, which hinders the comparison between study years because the changes from one year to the next could be due to age-related conditions. To minimise this bias, analysis of nonfatal digestive perforations and haemorrhages were conducted using the age of the patient at event occurrence. Nevertheless, the magnitude of NSAID use increase cannot be solely attributable to age-related conditions due to the short time span of the study. Utilisation of over-the-counter drugs is not recorded in the databases that were used for this study and thus was not taken into consideration; however, it is unlikely that the increase in nonfatal digestive perforations and haemorrhage rates reported here could have been attributable to nonprescription NSAIDs since there has been no change in their availability, which could have modified in one way or another consumption patterns over the study period.

Conclusion

The introduction of selective NSAIDs has had a major impact on prescribing practices and on the prevalence of nonfatal digestive perforations and haemorrhages in the presence of NSAIDs. Although some studies report that selective NSAIDs might have a better GI-safety profile compared with nonselective NSAIDs, they are not exempt of GI risk.[12,19] Claimed GI safety of selective NSAIDs prompted their use by a larger proportion of persons at risk for GI complications and for longer treatment periods. From a public health perspective, it is important to point out that the increase in the prevalence of NSAID use has coincided with a dramatic increase in the relative numbers of nonfatal digestive perforations and haemorrhages in the presence of NSAIDs. Therefore, selective NSAIDs should be prescribed with caution to persons at risk for GI complications, and other NSAID-induced adverse effects, including cardiovascular, cerebrovascular and renal complications, should also be taken into consideration when prescribing anti-inflammatory treatment.

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