Outcome of upper gastro-intestinal bleeding and use of ibuprofen versus paracetamol

• William J. Blot, Thomas Fischer, Gunnar Lauge Nielsen, Søren Friis, Michael Mumma, Loren Lipworth, Raymond DuBois, Joseph K. McLaughlin and Henrik T. Sørensen

Pharm World Sci 2004; 26: 319–323.

W.J. Blot, M. Mumma, L. Lipworth, J.K. McLaughlin: International Epidemiology Institute, Rockville, Maryland, USA
R. Dubois: Vanderbilt University Medical Center, Nashville, Tennessee, USA
T. Fisher, G.L. Nielsen: Department of Clinical Epidemiology, Aarhus and Aalborg University Hospitals, Aalborg, Denmark
H.T. Sørensen (correspondence, e-mail: hts@soci.au.dk): Department of Clinical Epidemiology, Aarhus; Aalborg University Hospitals, Aalborg, and Medical Department V, Aarhus University Hospital, Aarhus, Denmark
T. Fischer: Department of Cardiology, Aalborg University Hospital, Aalborg, Denmark
G.L.Nielsen: Department of Gastroenterology, Aalborg University Hospital, Aalborg, Denmark
S. Friis: Danish Cancer Society, Copenhagen, Denmark

Key words
Adverse drug reactions
Analgesics
Cohort
GI bleeding
Hemorrhage
Ibuprofen
NSAIDS
Paracetamol
Peptic ulcer

Abstract
Background: Nonsteroidal anti-inflammatory drugs (NSAIDs) are known to increase the risk of upper gastrointestinal bleeding (UGIB). Whether the severity of outcome of UGIB associated with NSAIDs differs from non-NSAID-related UGIB is less clear.
Method: Medical records of 228 patients hospitalized for UGIB in the Danish county of North Jutland were evaluated. Preadmission characteristics and clinical outcomes were compared between 112 patients who had been prescribed ibuprofen and 116 patients who had been prescribed paracetamol within 90 days of the hospitalization.
Results: The baseline characteristics of UGIB patients prescribed ibuprofen tended to differ from those prescribed paracetamol. The ibuprofen group significantly less often had histories of ulcer (11% vs 36%) and dyspepsia (19% vs 44%), or had been prescribed medications for these or other conditions, and had lower co-morbidity indices. Ibuprofen users also were somewhat less likely (31% vs 37%) to report GI pain at admission, but among hospitalized patients with endoscopic examinations were more likely (75% vs 58%) to be diagnosed with ulcer or hematemesis vs normal or gastritis/dyspepsia/reflux. For the clinical outcomes, 30 days case fatality rates were 12% for both ibuprofen and paracetamol users. The ibuprofen-related cases of UGIB more often required surgery (11% vs 3%) or transfusions (66% vs 57%), and those prescribed ibuprofen averaged 11 days in hospital, 4 days longer than those prescribed paracetamol. Adjustment for baseline characteristics and underlying conditions, or analyses eliminating patients with unconfirmed diagnoses and prior ulcers or restricted to patients with current hospital diagnoses of ulcer or hematemesis, did not materially alter the ibuprofen vs paracetamol differences in outcome measures. Generally similar results were obtained when restricting the analyses to patients prescribed ibuprofen or paracetamol within 30 days of UGIB hospitalization, except for a reduction in the 30 days case fatality rate among those prescribed ibuprofen.
Conclusions: UGIB patients with antecedent ibuprofen prescriptions experienced about the same case fatality rates, but more surgery and longer hospital stays, than patients prescribed paracetamol. The differences appear in part due to differing characteristics among those prescribed ibuprofen compared with those prescribed paracetamol, but also raise the possibility of drug-related effects.

Accepted February 2004

Introduction

It has been known for over a decade that use of nonsteroidal anti-inflammatory drugs (NSAIDs) can result in increased risk of upper gastro-intestinal bleeding (UGIB)[1-3]. Numerous epidemiologic studies have documented that rates of UGIB are elevated (about four-fold on average) among persons taking aspirin and non-aspirin NSAIDs[1-3]. Variation in risk with the dose and type of medication has been shown, but all forms and doses appear to result in some elevation in risk[1–3]. What is less clear is whether NSAID-related UGIB differs in severity from non-NSAID-related UGIB, with the few outcome studies producing conflicting results [4–12]. To address this issue we examined outcomes (death, surgery, transfusions and length of hospital stay) among persons hospitalized for UGIB who were prescribed ibuprofen, the most commonly used NSAID, and compared them with outcomes among a control group of persons hospitalized for UGIB prescribed the non-NSAID analgesic paracetamol.

Method

UGIB case ascertainment

We conducted a medical record review among residents of North Jutland, a Danish county of nearly 500,000 inhabitants, who had been hospitalized for UGIB during 1991–1995. The UGIB patients were identified from the Hospital Discharge Registry (HDR), a computerized database containing information on all admissions to somatic hospitals in the county from 1977 through 1995[13]. For each hospitalization, the files of the HDR include information on the personal identification number of the patient, date of discharge, and up to 20 discharge diagnoses, coded according to the Danish version of the International Classification of Diseases, 8th revision until the end of 1993 and 10th revision thereafter. UGIBs were defined as a diagnosis of esophagitis (ICD-8, 530.98; ICD-10, no code), gastritis (535.01; K29.0), gastric (531.90, 531.92, 531.95; K25.0, K25.2, K25.4, K25.6), duodenal (532.90; K26.0, K26.2, K26.4, K26.6), gastroduodenal (533.90; K27.0, K27.2, K27.4, K27.6) or gastrojejunal ulcer (534.90; K28.0, K28.2, K28.4, K28.6), hematemesis (784.59; K92.0), melaena (785.79; K92.1) or GI hemorrhage without specification (K92.2). Eligible for study were patients with a first diagnosis of UGIB during 1991–1995, with those with a prior UGIB hospitalization during 1977–1990 excluded. Also excluded were persons with prior hospitalizations for certain conditions which may predispose to UGIB, namely alcoholism (303; F10), esophageal varices (456.00–09; I85, I98.2), Mallory–Weiss syndrome (530.97; K22.6), or liver cirrhosis (571, 573; K70, K72-74, K76). Finally, since cancer is also a predisposing condition for UGIB, we excluded persons recorded in

the Danish Cancer Registry with an incident cancer after 1980.

Drug use

The computerized population-based Pharmaco-Epidemiologic Database of North Jutland[14] was used to identify prehospitalization prescriptions for ibuprofen and (for comparison) paracetamol among the UGIB patients. This database contains information on prescriptions dispensed during 1991–1995 from all pharmacies in the county. Medications dispensed during hospital stays are not recorded. Neither are over-the-counter sales of aspirin, paracetamol, and 200 mg ibuprofen, unless specifically prescribed by a physician for a chronic condition or unless prescribed to pensioners, in which case the government reimburses 50% of the cost of the drug. For 400-mg and 600-mg ibuprofen doses, and for all other non-aspirin NSAIDs, there is an unconditional 50% reimbursement. Data items in the prescription database include the unique personal identification number of the patient, type of drug prescribed according to the anatomical therapeutical chemical (ATC) classification system, date of prescription (date of dispensing the drug), tablet size, number of tablets in the package and number of packages. In addition to ibuprofen (ATC code M01 A E01) and paracetamol (N02 BE01), we identified persons prescribed other non-aspirin NSAIDs (azapropazone, diclofenac, etodolac, fenbufen, fenoprofen, flurbiprofen, indomethacin, ketoprofen, ketorolac, nabumetone, naproxen, phenylbutazone, piroxicam, proquazon, sulindac, tenoxicam, tiaprofenic acid, tolfenamic acid, tolmetin) and other drugs which may affect the risk of UGIB (namely, corticosteroids, anticoagulants, and high- or low-dose aspirin, serotonin reuptake inhibitors (N06AB), calcium-channel blockers (C08), nitroglycerine (C01D), and proton pump inhibitors (A02B).

Selection of patients

Selected for the ascertainment and review of medical records were all eligible UGIB patients who had been prescribed ibuprofen, but not other NSAIDs, aspirin, corticosteroids or anticoagulants within 90 days prior to the hospitalization for UGIB. Selected for comparison were eligible patients hospitalized with UGIB and prescribed paracetamol, but not NSAIDs or the other drugs, within 90 days prior to the hospitalization. The relevant hospitals were visited and medical records pertinent to the hospitalization for UGIB were obtained.

Outcome data

The records were abstracted by a single physician using a standardized form to record information on patient characteristics prior to and at admission, disease diagnosis, and outcomes of the hospitalization. The specific outcomes evaluated were: in-hospital case fatality; need for surgery; need for transfusion; and length of hospital stay.

Statistical analysis

Statistical analyses focused on comparisons of the preadmission, at admission, and in hospital procedures and outcomes among the UGIB patients prescribed ibuprofen compared with paracetamol. Differences in proportions between the two groups were tested for significance using Mantel–Haenzel test statistics, and logistic regression analyses were employed for estimating (via calculation of odds ratios) and testing group differences in hospital procedures and outcomes overall and after adjusting for age, the preadmission characteristic of history of prior ulcer, and the underlying endoscopic diagnosis (ulcer/hematemesis vs gastritis/dyspepsia/reflux/normal/unknown)[15,16]. Additional analyses adjusted for prior dyspepsia, use of tobacco and/or alcohol, and a co-morbidity index, whereby we classified individuals into three categories based on their number and severity of up to 19 coexistent health conditions[17]. In addition, analyses were repeated after excluding persons where documentation confirming the UGIB diagnosis was not found in the medical records, after restricting the subjects to those with endoscopically confirmed ulcer or hematemesis, and after deleting individuals with a history of prior ulcers. Finally, we repeated the analyses applying a 30-day exposure window for prescription of ibuprofen or paracetamol prior to hospitalization for UGIB.

Results

Overall, 112 UGIB patients had been prescribed ibuprofen (but not other UGIB-related drugs) and 116 paracetamol (but not other UGIB-related drugs) in the 90 days prior to their hospitalization for UGIB. Medical records were obtained for all but one ibuprofen and three paracetamol patients. About 60 % of the patients were female. The patients tended to be elderly, with more than 40 % in each group age 80 or above at admission (Table 1) with a tendency towards higher age in the paracetamol group.

The UGIB patients who were prescribed ibuprofen less often had a history of ulcer or dyspepsia recorded in the medical record ($P < 0.01$) or had been prescribed a proton pump inhibitor ($P < 0.01$), but were non-significantly more often listed as tobacco smokers and alcohol drinkers (Table 1). The ibuprofen group also somewhat less often had cardiovascular, central nervous system or any type of medication listed in the medical records.

At the time of admission, 31% of the records for ibuprofen users vs 37% for paracetamol users listed GI pain as a symptom. The ibuprofen cases tended to have fewer co-morbid conditions, as indicated by lower co-morbidity index scores. Endoscopy was performed for nearly equal percentages (65% and 66%) of the ibuprofen and paracetamol related cases, respectively. Among those with endoscopies, the ibuprofen group significantly ($P = 0.04$) more often had an endoscopic diagnosis of ulcer or haematemesis (75% vs 58%) than normal or gastritis/dyspepsia/reflux. For 14 (13%) ibuprofen and 22 (19%) paracetamol cases the diagnosis of UGIB could not be confirmed based on our review of medical records.

Thirty days case-fatality rates were equal in both groups (Table 2). The severity of outcome was greater for ibuprofen users for the three other outcome measures examined. The ibuprofen group more often (11% vs 3%) required surgery (adjusted OR = 2.2, 95% CI 1.1–4.3) and transfusions (66% vs 57%, adjusted OR = 1.2, 95% CI 0.9-1.6). The mean and median duration of stay in hospital were 11.4 and 8 days, respectively, for those in the ibuprofen group vs 7.4 and 5

days for those in the paracetamol group, with the OR rising with increasing number of days in hospital. The odds ratios in Table 2 were adjusted for age, previous ulcer and underlying diagnosis. Separate analyses adjusting for dyspepsia, use of tobacco or alcohol, or the co-morbidity index resulted in similar findings.

The four outcomes measures were correlated, with duration in hospital, frequency of transfusion, and case fatality rates being higher among those who underwent surgery than among those who did not. However, the longer hospital stays and higher transfusion rates among the ibuprofen than paracetamol group persisted among both those with and without surgery, as did the absence of a higher case fatality rate among ibuprofen users.

After the exclusion of 36 patients whose UGIB diagnosis was not confirmed, the relative differences remained largely unaffected, although the percentages with surgery and transfusions and the average length of hospital stay increased somewhat for both groups.

Similarly, restricting analyses to persons with endoscopically confirmed diagnoses of ulcer or hematemesis (namely, the 49% of the ibuprofen and 40% of the paracetamol groups shown in Table 2) again generally resulted in only minor changes in the ibuprofen vs paracetamol differences. In this subset of the cases, 36% of the ibuprofen vs 20% of the paracetamol group had hospital stays of 10 days or more. Case fatality rates were lower among ibuprofen cases with vs without endoscopic diagnoses of ulcer/hematemesis, whereas little difference was found among the paracetamol cases. Restricting analyses to persons without prior ulcers also yielded little change in results.

Using a 30-day exposure window prior to UGIB hospitalization yielded study groups of 63 patients with antecedent ibuprofen prescriptions and 70 patients with paracetamol prescriptions. There was almost no change in the results for the paracetamol group, and no significant changes for the ibuprofen group, although the 30-days case-fatality rate among those prescribed ibuprofen within 30 days of hospitalisation was 6% (n = 4) and was 18% (n = 9) among those prescribed ibuprofen 31 to 90 days prior to hospitalisation whereas patient characteristics and secondary outcomes remained largely unaltered.

Table 1 *Admission characteristics of GI bleeding patients prescribed ibuprofen vs paracetamol prior to hospitalization*

Characteristic (percentage)	*Paracetamol (n=116)*	*Ibuprofen (n=112)*
Female sex	60	62
Age < 65	15	21
65-79	40	36
80+	46	43
History of dyspepsia	44	19*
History of ulcer	36	11*
Use of proton pump inhibitors	13	1*
Use of cardiovascular drugs	59	50
Use of CNS drugs	41	34
Use of any medication	87	76
Smoking	21	31
Comorbidity index: 0	28	45**
Comorbidity index: 1	41	35**
Comorbidity index: 2+	31	21**
Alcohol drinker	12	18
GI pain reported	37	31
Endoscopic diagnosis:normal	12 (18)[a]	9 (14)[a]
– Gastritis/dyspepsia/reflux	16 (24)[a]	7 (11)[a]
– Ulcer/haematemesis	40 (58)[a]	49 (75)[a]
– Missing	34	35

* $P < 0.01$; ** $P < 0.05$.
[a]Percentages among those with performed endoscopies in parentheses.

Discussion

In this study UGIB patients prescribed ibuprofen within 90 days of hospitalization experienced the same 30 days case fatality rate as those prescribed paracetamol. When we restricted the exposure period to 30 days, the case fatality rate declined among patients prescribed ibuprofen, but the numbers of events were small. Irrespective of exposure window, ibuprofen cases more often underwent surgery and transfusions and spent significantly more days in hospital than paracetamol cases.

A limited number of other studies have examined these outcomes in NSAID related vs NSAID unrelated cases of UGIB, with inconsistent results. Among 785 upper- and 161 lower-GIB cases in the United States, UGIB patients who had taken NSAIDs had lower in-hospital mortality rates (5% vs 13%), less rebleeding, and a one-day shorter median hospital stay than those who had not taken NSAIDs, while no significant differences were observed among NSAID users with lower GIB[4]. A few studies have indicated no substantial differences in outcome of NSAID-related UGIB cases. A review of Spanish UGIB patients showed that persons prescribed NSAIDs less often had prior ulcers and that the bleedings resulted more often from gastric vs duodenal ulcers, but reported no differences in clinical outcomes, including surgery, transfusion, and length of hospital stay[5]. Similarly, studies of 80 ulcer patients in Australia[6] and 150 in the United States[7] found no NSAID effect in case fatality, and a study of nearly 600 patients in a multi-center study in the United States, Sweden and Hungary[8] found little difference in clinical presentation or in rates of surgery between NSAID-related vs unrelated cases. Some studies, however, have reported poorer outcomes for NSAID-related UGIB diagnoses. In a recent prospective follow-up of Dutch UGIB patients, those who had been prescribed NSAIDs had significantly higher in-hospital mortality (9% vs 4%), rebleeding and need for surgery than those not prescribed these medications[9]. Case fatality rates also were at least twice as high among NSAID-related than non-NSAID-related peptic ulcer cases in earlier studies of over 200 patients in each of the United Kingdom[10] and United States[11], with a nearly 4-fold increase in surgery in the US study. In New Zealand, morbidity and mortality rates were similar, but a three-day longer median hospital stay was reported for patients with NSAID-related bleeding ulcers[12].

Part of the difficulty in evaluating the relationship between drug use and clinical outcomes arises from the differing profiles of persons prescribed various

medications, which could generate confounding by indication. The ibuprofen group in our study was younger, less likely to have had a prior history of ulcer or dyspepsia, or to have been prescribed anti-ulcer drugs. These differences are not surprising, however, given usual Danish medical practice. A history of ulcer or dyspepsia is regarded as relative contraindication to prescription of NSAIDs. Gastroprotection through concomitant use of proton pump inhibitors or misoprostol was not generally used in the study period. The most commonly used alternative analgesic, not known to be associated with adverse GI effects, is paracetamol. On this background the 11% prevalence of reported prior ulcers among the ibuprofen group (although substantially lower than the 36% among the paracetamol group) might be considered high. However, since by study design we excluded persons with hospitalization for bleeding ulcer before the 1991–1995 study period, the prior ulcers reported in the medical records likely represent less serious conditions treated in doctors' offices or on an out-patient basis.

Although fewer among the ibuprofen than paracetamol groups had prior episodes of ulcer, some of the outcomes (although not the most definitive outcome, namely case fatality) were poorer. The poorer secondary outcomes seem at least in part associated with more severe findings at endoscopy in the ibuprofen group where only 25% had a diagnosis of gastritis, dyspepsia, reflux or normal vs 42% among the paracetamol group. However, adjusting for such differences (either statistically through the regression models or by eliminating those with normal or unconfirmed UGIB diagnoses or by restricting analyses to those with endoscopically confirmed ulcer) failed to eliminate the differences in outcomes between the two groups. It is possible that residual confounding may have hindered our adjustment capacity. Nevertheless, of particular note is the four day longer average (and three day longer median) hospital stay among the ibuprofen group, which remained largely the same in all analyses.

In the primary analyses we applied a 90-day exposure window for antecedent prescriptions of ibuprofen and paracetamol. Although NSAID prescriptions within 90 days prior to hospitalization have been shown in this population to be significantly related to increased UGIB risk[18], this relatively long exposure period may increase the possibility of misclassification of exposure. This misclassification may have tended to dampen rather than accentuate the differences between the ibuprofen and paracetamol groups, however, for all but 30 days case fatality, the results were similar in the 30-day and 90-day analysis. The lower case fatality among the ibuprofen group when using the 30-day exposure window is compatible with a higher general morbidity among chronic users of paracetamol. A similar pattern might have been expected in the 90-day analysis, but the opposite was observed as case fatality was higher among the ibuprofen subset who received prescriptions 31 to 90 days prior to hospitalisation. The explanation for the this difference is unclear, but seems most likely related to random fluctuations from the mortality results based on small numbers in each subset.

Our adjustment for tobacco and alcohol intake as well as prior ulcer reflected in medical records had little impact on the observed ibuprofen vs paracetamol differences in outcome measures. Regarding use of other drugs with ulcerogenic potential we found no difference in use of serotonin reuptake inhibitors, whereas the use of nitroglycerine and Ca-blockers was highest in the paracetamol group reflecting the higher general morbidity.

We did not have data on infection with helicobacter pylori or on specific medical regimes during hospital stay. However, most hospitals have standardized guidelines for medical treatment of ulcer disease irrespective of previous drug exposure and variation in medical treatment is thus unlikely to have distorted our associations.

The strengths of our study include the examination of the total population in one area of Denmark, representation of all socioeconomic groups, and use of the Hospital Discharge Register which encompassed all serious UGIB events in the population. From the North Jutland Pharmaco-Epidemiologic Prescription Database we obtained complete ascertainment of all use of prescription NSAIDs thus avoiding reliance upon self-reported analgesic use. Through these population-based resources we believe we have minimized problems that can sometimes afflict case-control studies or cohorts of selected groups of patients.

Conclusions

In summary, this investigation revealed a lower 30-days case fatality in patients prescribed ibuprofen in

Table 2 *Hospital outcomes of GI bleeding patients prescribed ibuprofen vs paracetamol*

Outcome (percentage)	*Paracetamol (n=116)*	*Ibuprofen (n=112)*	*Odds ratio**	*95% CI*
Died within 30 days	12	12	1.0	0.7–1.6
Had surgery	3	11	2.2	1.1–4.3
Had transfusion	57	66	1.2	0.9–1.6
Length of stay (days)				–
– < 5 days	49	34	1.0	–
– 5–10 days	30	30	1.4	0.9–1.5
– 10+ days	21	36	2.7	1.2–5.9
– median, days	5	8		

* Prevalence adds ratio for outcome among ibuprofen relative to paracetamol users adjusted for age group (<65, 67–79, 80+), prior ulcer (yes/no), and underlying diagnosis (ulcer-hematemesis vs other).

the preceding month but no difference when examining drug exposure 90 days prior to hospital admission. Ibuprofen-related UGIB was associated with more surgery and transfusions and longer hospital stay than non NSAID-related UGIB. The differences may relate to differing characteristics of patients prescribed ibuprofen compared with paracetamol. However, the persistence of group differences after adjusting for preadmission characteristics and underlying endoscopic diagnoses raises the possibility of drug effects. It could be speculated that NSAIDs are more effective in masking GI pain, thus resulting in delayed admission and greater need for surgery, transfusion and longer hospitalization for recovery. If our findings are confirmed in other populations, the public health impact of NSAID-induced UGIB may be greater than previously recognized.

Acknowledgements

The computerized databases used are supported by the Western Danish Research Forum for Health Sciences (Vestdansk Forskningsforum). Financial support for the International Epidemiology Institute was provided by a grant from GlaxoSmithKline.

References

1 Hawkey CJ. Non-steroidal anti-inflammatory drugs and peptic ulcers. BMJ 1990; 300: 278–84.

2 Gabriel S, Jaakkimainen L, Bombardier C. Risk for serious gastrointestinal complications related to use of nonsteroidal anti-inflammatory drugs: a meta-analysis. Ann Intern Med 1991; 115: 787–96.

3 Hernandez Diaz S, Garcia Rodriguez LA. Association between nonsteroidal anti-inflammatory drugs and upper gastrointestinal tract bleeding/perforation: an overview of epidemiologic studies published in the 1990s. Arch Intern Med 2000; 160: 2093–9.

4 Wilcox CM, Clark WS. Association of nonsteroidal antiinflammatory drugs with outcome in upper and lower gastrointestinal bleeding. Dig Dis Sci 1997; 42: 985–9.

5 Llorente Melero MJ, Tenias Burillo JM, Del Val Antonana A, Zaragoza Marcet A. Influence of nonsteroidal anti-inflammatory drugs on clinical course in upper gastrointestinal tract bleeding. Rev Esp Enferm Dig 1999; 7: 497–507.

6 Henry DA, Johnston A, Dobson A, Duggan J. Fatal peptic ulcer complications and the use of non-steroidal antiinflammatory drugs, aspirin, and corticosteroids. BMJ 1987; 295: 1227–9.

7 Bliss DW, Stabile BE. The impact of ulcerogenic drugs on surgery for the treatment of peptic ulcer disease. Arch Surg 1991; 126: 609–12.

8 Laszlo A, Kelly JP, Kaufman DE, Sheehan JE, Retsagi G, Wilholm BE et al. Clinical aspects of upper gastrointestinal bleeding associated with use of nonsteroidal antiinflammatory drugs. Am J Gastroenterol 1998; 93: 721–5.

9 Vreeburg EM, de Bruijne HW, Snel P, Bartelsman JH, Rauws EA, Tytgat GN. Previous use of non-steroidal anti-inflammatory drugs and anticoagulants: the influence on clinical outcome of bleeding gastroduodenal ulcers. Eur J Gastroenterol Hepatol 1997; 9: 41–4.

10 Armstrong CP, Blower AL. Non-steroidal anti-inflammatory drugs and life threatening complications of peptic ulceration. Gut 1987; 28: 527–32.

11 Peoples JB. Peptic ulceration and the nonsteroidal anti-inflammatory drugs. Am Surg 1985; 51: 358–62.

12 Keating J, Chandran H. Antiinflammatory drugs and emergency surgery for peptic ulcers in the Waikato. NZ Med J 1992; 105: 127–9.

13 Andersen TF, Madsen M, Jorgensen J, Mellemkjaer L, Olsen JH. The Danish National Hospitalization Register: valuable resource data for modern health sciences. Dan Med Bull 1999; 46: 263–4.

14 Nielsen GL, Sorensen HT, Zhou W, Steffensen FH, Olsen JH. Pharmacologic prescription database of North Jutland: a valid tool in pharamacoepidemiologic research. Int J Risk Safety Med 1997: 10: 203–5.

15 Breslow NE, Day NE. Statistical methods in cancer research. Vol 1. Analysis of case-control studies, IARC Sci Pub 32. Lyon, France, 1980.

16 Statistical Analysis System, Cary North Carolina; 2001.

17 Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chron Dis 1987; 40: 373–83.

18 Mellemkjaer L, Blot WJ, Sorensen HT, Thomassen L, McLaughlin JK, Nielsen GL et al. Upper gastrointestinal bleeding among users of NSAIDs: a population-based cohort study in Denmark. Br J Clin Pharmacol 2002; 53: 173–81.