Study protocol: Risk of uncomplicated peptic ulcer in the general population

BACKGROUND

We propose to use the Health Improvement Network database (THIN) to provide new data the on relative risk of uncomplicated symptomatic peptic ulcer (UPU) associated with the use of low-dose ASA, other anti-inflammatory drugs (NSAIDs, steroids) and other risk factors. We will also evaluate the role of dose and duration of drug treatment in the risk of UPU and estimate this risk separately for gastric and duodenal ulcer.

STUDY OBJECTIVES

1-To estimate the relative risk of UPU associated with use of low dose ASA and other anti-inflammatory drugs (NSAIDs, steroids) in the general population

2- To estimate the dose-response and duration-response associated with use of these drugs

3- To estimate the relative risk of UPU associated with naïve/non-naïve use of low dose ASA in the general population

4- To evaluate the effect of proton pump inhibitors (PPI) (alone or in combination with anti-inflammatory drugs) on the occurrence of UPU in the general population

5-.To investigate the management of low dose ASA/OAP after UPU

METHODS

Design

A retrospective cohort study with nested case-control analysis will be performed using data from the THIN database in the UK.

Source population:

THIN database, which contains computerized information entered by general practitioners in the UK (1). Data on about 4 million patients are systematically recorded and sent anonymously to THIN. THIN collects and organizes this information in order to be used for research projects. The computerized information includes demographics, details from general practitioner's visits, diagnoses from specialist's referrals and hospital admissions, results of laboratory tests and a free text section. Prescriptions issued by the general practitioner are directly generated from the computer. An additional requirement for participating practices is recording of the indication for

new courses of therapy. The READ classification is used to code specific diagnoses, and a drug dictionary based on data from the MULTILEX classification is used to code drugs (2,3).

Study cohort

The study cohort was identified in a previous cohort study using this database (4). Briefly, we identified all patients 40-84 years old between January 1997 and December 2005 with a registration status of permanent or died after the practice was up-to-standard. Patients became members of the study cohort on the first day of the study period when they met the criteria of at least two years enrollment with the general practitioner and one year of computerized prescription history. That date was their beginning date. Patients with a code for cancer, peptic ulcer (both uncomplicated and complicated), upper GI bleeding, oesophageal varices, Mallory-Weiss disease, alcohol abuse, liver disease or coagulopathies before beginning date were excluded from the study cohort. Finally, we excluded persons 65 years and older at beginning date with a follow-up greater than one year and no recording of data during their whole period of follow-up (proxy for incomplete data recording). All remaining patients constituted the final study cohort.

Ascertainment of cases with uncomplicated peptic ulcer

Case ascertainment (but not control selection) was done in a previous study (4). Briefly, all members of this study cohort contributed person time until the detection of peptic ulcer, any exclusion criteria (i.e., code for cancer, upper GI bleeding, oesophageal varices, Mallory-Weiss disease, alcohol abuse, liver disease or coagulopathies), their 85th birthday, death, or end of study period (December 2005), whichever came first.

After the initial computerized search for codes suggesting UPU, we identified 5320 potential cases. We considered a patient to have uncomplicated peptic ulcer if the clinical diagnosis of peptic ulcer is made during a specialist visit or hospitalization (most likely by endoscopic examination, the standard diagnostic technique in the UK) and the specific site of the ulcer is located in the stomach or duodenum. Patients with complicated peptic ulcer (either bleeding or perforation) were excluded. After the review of the patient profiles, we finally identified 3923 incident cases of UPU. (4)

Patients have been classified according to site of the ulcer into gastric, duodenal and multiple site, and according to their Helicobacter pylori status into positive, negative, or unknown. The date of first clinical diagnosis of UPU as recorded in the computerized medical records will be considered as index date.

Control selection

Ten thousand controls frequency-matched to cases by age (within 1 year), gender and calendar year will be randomly sampled from the entire study cohort that gave rise to the cases of uncomplicated PU so that the likelihood of being selected as a control will be proportional to the

person-time at risk. Specifically, a date during the study period will be generated at random for each of the members of the study population. If the random date of a study member is included in his or her eligible person-time, we will use his or her random date as the index date and mark that person as an eligible control. The same exclusion criteria will be applied to controls as to cases. Ten thousand controls, frequency-matched to cases by age (within 1 year), gender and calendar year will be randomly selected from the pool of eligible controls

Statistical analysis

To determine the association between UPU and the use of drugs (ASA, NSAIDs, PPIs and steroids) or between UPU and alcohol and tobacco consumption, we will run unconditional logistic regression models and compute the odds ratios (ORs) and their 95% confidence intervals (95%CI). In this nested case control analysis we will use the 3923 incident cases of UPU and the 10000 controls. Owing to the selection process of controls, ORs are unbiased estimates of rate ratios in the underlying study cohort. All estimates will be adjusted for the frequency-matched variables (age, sex, calendar year), follow-up time BMI, GP visits, referrals, and other known risk factors for UPU.

Drug exposure definition

The exposures of interest will be low dose ASA, NSAIDs, PPIs, steroids, alcohol and tobacco. ,We will define four time windows of exposure: current use, recent use, past use and non use. *Current use* will refer to use that lasts until the index date based on the length of drug therapy as prescribed by the general practitioner or fall within the 7 days prior to the index date. *We will evaluate whether the risk is constant between the first week before index date and week 2 to 4: if estimates of risk appear to be relatively homogenous between these 2 windows we will accordingly extend the window defintion of current use to use in the month prior to the index date. Recent use* will be use that ended between 7 and 31 days prior to the index date. *Past use* will be use ending between 31 and 365 days before the index date. Finally, the time window of *non-use* will be defined as no use of the drug of interest in the 365 days before the index date. Low dose ASA users will be classified in naive/non-naive users. Naïve use will be defined as first use in the study period that was not preceded by an earlier ASA prescription in the previous year.

Management of low dose ASA after UPU

Additionally we will investigate the management of low dose ASA among cases of UPU. Thus we will classify individuals according to low ASA exposure before and after UPU episode. We will estimate the rate of discontinuation stratified by age, sex, UPU site and H. pylori status. Additionally we will run an unconditional logistic regression analysis to explore these and other potential predictors of stopping low dose ASA such as previous comorbidity, PPI use, etc...

References:

1. Bourke A, Dattani H, Robinson M. Feasibility study and methodology to create a quality-evaluated database of primary care data. Informatics in Primary Care 2004;12:171-7.
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