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Risk of seizure associated with use of acid-suppressive drugs: An observational cohort study

María E. Sáez [a,b], Antonio González-Pérez [a,b], David Gaist [c,d], Saga Johansson [e], Péter Nagy [e], Luis A. García Rodríguez [a,*]

[a] Spanish Centre for Pharmacoepidemiologic Research (CEIFE), Madrid, Spain
[b] Andalusian Bioinformatics Research Centre (CAEBi), Seville, Spain
[c] Department of Neurology, Odense University Hospital, Odense, Denmark
[d] Department of Clinical Research, Faculty of Health Sciences, University of Southern Denmark, Odense, Denmark
[e] AstraZeneca Gothenburg, Mölndal, Sweden

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ABSTRACT

Objectives: Previous, large, prescription-event monitoring studies in patients receiving PPI therapy recorded instances of convulsion or seizure. The objective of this study was to quantify the relative risk of seizure associated with the use of proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H_2RAs) in a general population, overall and stratified by epilepsy status, and to determine the effects of demographics and comorbidities.

Methods: In this observational study (NCT01744301), patients aged 20–84 years in the study period from 1 January 2005 to 31 December 2011 were identified from The Health Improvement Network. In a nested case–control analysis, 8605 patients with seizure were matched to 40 000 controls. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using logistic regression.

Results: After adjustment, there were no associations between current PPI use and seizure risk in the overall population (OR: 1.05; 95% CI: 0.87–1.27), the subcohort with epilepsy (OR: 0.87; 95% CI: 0.49–1.53), and the subcohort without epilepsy (OR: 1.05; 95% CI: 0.87–1.28). There were no associations between current H_2RA use and seizure risk in the overall population (OR: 1.16; 95% CI: 0.62–2.18) and the subcohort without epilepsy (OR: 1.02; 95% CI: 0.51–2.01). Seizures were less frequent in women than in men. Dementia/psychosis, anxiety, depression, and use of anxiolytics, antidepressants, and paracetamol were associated with an increased seizure risk.

Conclusions: Our study revealed that the use of PPIs and the use of H_2RAs were not associated with an increased risk of seizures in the overall population or in the cohorts stratified by epilepsy status.

1. Introduction

Proton pump inhibitors (PPIs) are the mainstay of treatment for acid-related conditions such as gastroesophageal reflux disease and peptic ulcer disease. The efficacy and favorable safety profile of PPIs [1,2] and the large number of individuals potentially in need of acid-suppressive treatment [3–5] have made PPIs one of the most widely prescribed classes of drugs in clinical practice [6].

Long-term use of acid-suppressive treatment has helped to generate a large amount of effectiveness and safety data [7–12]. These data allow for the identification of uncommon adverse events that may be linked to acid-suppressive therapy, although careful analysis is required because at least some of the magnitude of increased risk seen in observational studies, when comorbid conditions cannot be fully adjusted for, is probably because of confounding [13–15].

In two of the three large prescription-event monitoring studies in patients receiving PPI therapy, instances of convulsion or seizure were recorded [8–10]. A study that included 16 204 patients treated with omeprazole recorded 17 convulsion events; in five of these events, the possibility of a link with omeprazole could not be excluded [10]. One patient with epilepsy as a new event was reported in a study of pantoprazole, which included 11 541 patients [9]. No seizures or convulsions were recorded as adverse events in a prescription-event monitoring study of 11 595 patients treated with esomeprazole [8].

Abbreviations: ASA, acetylsalicylic acid; CNS, central nervous system; CVA, cerebrovascular accident; H_2RAs, histamine-2 receptor antagonists; ICH, intracerebral hemorrhage; IS, ischemic stroke; PCP, primary care physician; PPIs, proton pump inhibitors; SAH, subarachnoid hemorrhage; TBI, traumatic brain injury; TIA, transient ischemic attack; THIN, The Health Improvement Network.

* Corresponding author at: Spanish Centre for Pharmacoepidemiologic Research (CEIFE), Almirante 28-2, E-28004 Madrid, Spain. Tel.: +34 91 531 6242; fax: +34 91 531 2871.
E-mail address: lagarcia@ceife.es (L.A. García Rodríguez).

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Events of convulsion or seizure were also recorded in a large histamine-2 receptor antagonist (H_2RA) postmarketing surveillance study [7]. The study included 9928 patients receiving cimetidine and 9351 controls. Major convulsion as a new event was recorded as a primary diagnosis in five patients using cimetidine and in three patients in the control group. No association between cimetidine therapy and epilepsy was documented.

An enduring predisposition for unprovoked seizures is a defining characteristic of epilepsy [16], but not all individuals who experience a seizure have epilepsy [17]. Acute, provoked seizures occur in close temporal sequence to systemic or brain insults, such as traumatic brain injury, cerebrovascular events, drug withdrawal, and infections [17]. Some drugs, including certain analgesics, anesthetics, and antipsychotics, can increase the risk of seizure occurrence [18]. Unprovoked seizures occur either in the absence of a potentially reversible clinical condition or outside the time interval used to estimate the occurrence of an acute symptomatic seizure [17].

AstraZeneca has received spontaneous postmarketing case reports of convulsion/seizure in patients taking PPIs, and as commonly observed in postmarketing report information regarding possible underlying cause, concomitant medication and potentially contributing factors were limited. Prior reports have indicated that omeprazole and esomeprazole treatments may give rise to pharmacokinetic interactions with antiepileptic drugs such as phenytoin. However, reports indicated decreased clearance of phenytoin of a small magnitude [19–21]. Importantly, the effect of such an interaction, if any, would be to increase the risk of adverse effects rather than seizures. A meta-analysis performed by Ogawa and Echizen revealed that omeprazole increased the AUC of phenytoin by 10% at most, and the change did not reach a statistically significant level ($p = 0.10$), indicating that any inhibitory effect of omeprazole on phenytoin metabolism would be small [21]. Thus, no known mechanism could explain an increased risk of seizures in patients taking PPI. We therefore conducted an epidemiological study aimed at testing whether the use of acid-suppressive drugs in a general population is associated with increased risk of seizure, both overall and stratified by epilepsy status. A further aim was to determine the effects of demographic and lifestyle factors, comorbidities, and other medications on the risk of seizures.

2. Materials and methods

2.1. Study design

This was a retrospective, observational cohort study with nested case–control analysis (ClinicalTrials.gov ID: NCT01744301). Data were collected from The Health Improvement Network (THIN) database in the UK. The study was approved by a Scientific Review Committee (12-048V).

2.2. Data source

The Health Improvement Network (THIN) is a computerized medical research database that contains systematically recorded, anonymized data on more than 4 million individuals currently registered with participating primary care practices in the UK. It is representative of the UK population in terms of age, sex, and geographical distribution. The validity of THIN for use in pharmacoepidemiological research has been demonstrated [22–24]. The Read classification was used to code specific diagnoses [25], and a drug dictionary based on data from the Gemscript classification was used to code drug prescriptions [26].

2.3. Study cohort

Patients who were aged 20–84 years in the study period from 1 January 2005 to 31 December 2011, who had been enrolled with their primary care physician (PCP) for at least 2 years, and who had a computerized prescription history of at least 1 year were identified. Patients had to have no history of cancer, drug or alcohol abuse, or alcohol-related disease and to have not received a prescription for acid-suppressing drugs (PPIs or H_2RAs) for at least 1 year. The earliest date on which an individual met all of these eligibility criteria within the study period was marked as the start date. Individuals aged 70 years or over who had been enrolled with their PCP for more than 1 year and had fewer than two health contacts during that time (proxy for incomplete data recording) were excluded. All remaining individuals constituted the final study cohort.

2.4. Case ascertainment

To identify cases of seizure, all members of the study cohort were followed up from their start date to the earliest of the following endpoints: diagnosis of seizure (for Read codes, see Online Table 1), meeting an exclusion criterion (cancer, alcohol abuse, alcohol-related disease, or drug abuse or reaching 85 years of age), death, or end of study period (31 December 2011). Patients who had seizures in the context of alcohol abuse, recorded in the month after the seizure onset, were not retained as cases.

A manual review of anonymized computerized profiles including free text comments of a sample of 595 potential seizure cases confirmed that inclusion was valid for 541 patients (90.9%). The main reasons for exclusion at manual review were as follows: alcohol or drug abuse, other classes of paroxysmal event or convulsion not classified as seizure (mainly vasovagal attack and myoclonic jerk), diagnosed malignant brain tumor, and unconfirmed event.

We classified the study cohort into a subcohort with epilepsy and a subcohort without epilepsy. The subcohort with epilepsy included all individuals in the study cohort with epilepsy codes (listed in Online Table 2) recorded before the start date or anytime during the study period (i.e., before the end of follow-up). All remaining individuals constituted the subcohort without epilepsy. The corresponding proportion of patients with confirmed seizure after manual review was 95.9% in the subcohort with epilepsy and 87.5% in the subcohort without epilepsy.

From the 541 seizure cases confirmed by manual review, we selected a random sample of 100 for secondary validation. Primary care physicians were asked to fill in questionnaires designed to obtain additional information about these patients. Completed questionnaires were returned for 86 patients, with PCPs ratifying a seizure diagnosis in 83.7% of the cases confirmed by manual review. The main reasons for exclusion were, as above, alcohol- or drug abuse-related seizures, event confirmed as other classes of paroxysmal event or convulsion, and unconfirmed occurrence of the event by the PCP.

We defined the index date as the date of the first recorded diagnosis of seizure during the study period. Referrals and hospitalizations in the 30 days before and 30 days after the index date were identified by computerized searches. Referrals and hospitalizations were classified as seizure-related if (i) they were specifically coded as neurological referrals, (ii) seizure and epilepsy codes were marked as referred in THIN, or (iii) nonspecific referral and hospitalization codes were recorded within 10 days from the index date.

Seizure cases were further classified into acute and unprovoked cases following the recommendations of Beghi et al. [27] Seizures were considered to be acute if a code for at least one of the following was recorded within 30 days before or after the index date: central nervous system (CNS) infection, traumatic brain injury (TBI), cerebrovascular accident (CVA), metabolic alterations (hypoglycemia, hyperglycemia, hyponatremia, hypocalcemia, hypomagnesemia), eclampsia, multiple sclerosis, or medicament poisoning/allergic reaction.

2.5. Nested case–control analysis

For the nested case–control analysis, all identified seizure cases ($n = 8605$) were matched by calendar-year and frequency to 40 000