European Journal of Internal Medicine 25 (2014) 701–709

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Original Article

Altered mental status in older adults with histamine2-receptor antagonists: A population-based study

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ARTICLE INFO

Article history:
Received 4 November 2013
Received in revised form 17 May 2014
Accepted 24 June 2014
Available online 16 July 2014

Keywords:
Histamine H2 antagonists
Altered mental status
Aged
Chronic renal insufficiency
Cohort studies
Risk

ABSTRACT

Background: Standard doses of histamine2-receptor antagonists (H2RAs) may induce altered mental status in older adults, especially in those with chronic kidney disease (CKD).
Methods: Population-based cohort study of older adults who started a new H2RA between 2002 and 2011 was conducted. Ninety percent received the current standard H2RA dose in routine care. There was no significant difference in 27 baseline patient characteristics. The primary outcome was hospitalization with an urgent head computed tomography (CT) scan (proxy for altered mental status), and the secondary outcome was all-cause mortality also within 30 days of a new H2RA prescription.
Results: Standard *vs.* low H2RA dose was associated with a higher risk of hospitalization with an urgent head CT scan (0.98% *vs.* 0.74%, absolute risk difference 0.24% [95% CI 0.11% to 0.36%], relative risk 1.33 [95% CI 1.12 to 1.58]). This risk was not modified by the presence of CKD (interaction *P* value = 0.71). Standard *vs.* low H2RA dose was associated with a higher risk of mortality (1.07% *vs.*0.74%; absolute risk difference 0.34% [95% CI 0.20% to 0.46%], relative risk 1.46 [95% CI 1.23 to 1.73]).
Interpretation: Compared to a lower dose, initiation of the current standard dose of H2RA in older adults is associated with a small absolute increase in the 30-day risk of altered mental status (using neuroimaging as a proxy), even in the absence of CKD. This risk may be avoided by initiating older adults on low doses of H2RAs for gastroesophogeal reflux disease, and increasing dosing as necessary for symptom control.

1. Introduction

Each year millions of patients in Canada are prescribed histamine2-receptor antagonists (H2RAs) for the treatment of gastroesophageal reflux disease [1]. Histamine2-receptor antagonists are also widely available without a prescription in many countries including Canada, implying that their use is even more widespread than prescription data suggests. A standard daily dose of a H2RA (ranitidine [Zantac] 300 mg/day or famotidine [Pepcid] 40 mg/day; usually divided into twice a day) is recommended in popular drug prescribing references for gastroesophageal reflux symptom control in patients of all ages when kidney function is preserved (Table 1) [2–5].

However, older adults have age-related changes in pharmacokinetics and pharmacodynamics such as reduced first-pass liver metabolism, as well as increased fat content and decreased body water that reduces a drug's volume of distribution (important with hydrophilic drugs such as H2RAs) [6,7]. Such changes can increase the risk of drug toxicities with standard dosing [6,7]. Furthermore, H2RAs undergo renal excretion, and older adults often experience an age-related decrease in glomerular filtration rate, even in the absence of kidney disease [8]. The loss of kidney function has been attributed primarily to a loss of glomeruli, tubular atrophy, interstitial fibrosis and arteriosclerosis [8]. As such, the current standard dose of H2RA in older adults may lead to adverse drug events such as mental status changes (e.g., confusion, hallucination) or arrhythmias (e.g., tachycardia, atrioventricular block) [4,5]. Older adults with bona fide chronic kidney disease may be the most vulnerable to H2RA toxicity from reduced renal elimination [9].

To date, hundreds of case reports from the United States Food and Drug Administration in addition to several literature reviews and prospective studies have noted the potential for H2RAs to induce an altered

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http://dx.doi.org/10.1016/j.ejim.2014.06.021
0953-6205/

Table 1
Histamine2-receptor antagonist dosing in popular drug prescribing references.

	Low dose[a]	Standard dose[a]	UpToDate recommendation	Compendium of pharmaceuticals and specialties
Famotidine	20 mg/day	40 mg/day	• 20 to 80 mg/day • Manufacturer recommends reduction by 50% in renal impairment	• 20 mg to 40 mg/day • Dosing should be reduced by half in patients with renal insufficiency
Ranitidine	150 mg/day	300 mg/day	• 300 to 600 mg/day • Oral dose should be 150 mg/day for renally impaired patients	• 150 mg taken twice daily or 300 mg once daily (in some cases up to 600 mg/day) • Recommended daily dose for patients with creatinine clearance <50 mL/min is 150 mg

[a] Low and standard dose as defined in this study.

mental status — which often precipitates hospitalization and death among the elderly [9–18]. For example, Slugg et al. conducted a small prospective convenience study of 41 inpatients to correlate ranitidine pharmacokinetics with the incidence of altered mental status and found 13 cases of ranitidine associated delirium (32%) primarily in the context of older age and kidney disease [13]. However, studies have generally been limited by the lack of data on outpatient H2RA use, relatively limited sample sizes, and a general lack of evidence to support the use of lower doses to reduce the incidence of altered mental status.

To inform this issue, we conducted a population-based cohort study to compare the 30-day risk of altered mental status and mortality in older adults initiated on an oral H2RA either at a standard dose or at a low dose in routine outpatient settings. We also investigated whether this association was modified by the presence of chronic kidney disease.

2. Methods

2.1. Setting and study design

Residents of the province of Ontario, Canada have universal access to hospital care and physician services. Those 65 years of age or older also have universal prescription drug coverage (approximately two million individuals in 2012) [19]. All health care encounters are recorded in databases held securely in a linked, de-identified form at the Institute for Clinical Evaluative Sciences (ICES) in Ontario, Canada. We conducted a population-based retrospective cohort study using these data sources. This study was conducted according to a pre-specified protocol that was approved by the research ethics board at Sunnybrook Health Sciences Centre (Toronto, Canada). The reporting of this study followed guidelines for observational studies (detailed in Appendix A) [20].

2.2. Data sources

We ascertained baseline characteristics, H2RA use and dose, and outcome data using eight linked healthcare databases. Demographic and vital status information on all Ontario residents who have ever been issued a health card is recorded in the Ontario Registered Persons Database. Detailed diagnostic and procedural information on all hospital admissions and emergency room visits is recorded in the Canadian Institute for Health Information Discharge Abstract Database and the National Ambulatory Care Reporting System, respectively. Health claims for inpatient and outpatient physician services are recorded in the Ontario Health Insurance Plan database. Diagnostic information on all individuals ever admitted to a mental health unit is available in the Ontario Mental Health Reporting System. Outpatient prescription drug information including the dispensing date, quantity of pills, dose, and number of days supplied is accurately recorded in the Ontario Drug Benefit Program database, with an error rate less than 1% [21]. In a subpopulation of patients, we used two linked laboratory data sets to obtain baseline serum creatinine values from the year prior to the new H2RA prescription (median 94 days). All data sources have been used previously to study drug safety [22–25]. With the exception of prescriber information, the databases were complete for all variables used in this study.

2.3. Patients

We established a cohort of all older adults in Ontario with evidence of a new outpatient prescription for oral ranitidine or famotidine between April 1, 2002 and December 31st 2011. Cimetidine prescriptions were not included in our study as they made up less than 1.5% of all H2RA prescriptions in our jurisdiction during the accrual period. All eligible prescriptions were either standard dose or low dose (Table 1). Patients with multiple eligible prescriptions could only enter the cohort once, and the date of the first H2RA prescription served as the patient's index date (cohort entry date; start of follow-up). We assessed baseline demographic characteristics, comorbid conditions (5 years prior to index date) and concurrent drug therapy (120 days prior to index date). We excluded the following H2RA users from the analysis: those in their first year of eligibility for prescription drug coverage (i.e., age 65 years; 5.8% of cohort) to avoid incomplete medication records; those discharged from hospital in the 2 days prior to the index date (5.7% of cohort) to ensure prescriptions were initiated in the outpatient setting; those with end-stage renal disease as dialysis may influence H2RA pharmacokinetics (1.0% of cohort); those with H2RA prescriptions in the 180 days prior to index date (to restrict the analysis to new H2RA initiations; 22.7% of cohort); and those living in long-term care facilities as such residents tend to have multiple comorbidities and may be more prone to altered mental status (6.7% of cohort) [26]. We identified individuals with chronic kidney disease using an algorithm of diagnosis codes validated in our region for older adults [27]. The algorithm identified patients with a median estimated glomerular filtration rate (eGFR) of 38 mL/min per 1.73 m^2 (interquartile range 27 to 52), whereas its absence identified patients with a median eGFR of 69 mL/min per 1.73 m^2 (interquartile range 56 to 82).

2.4. H2RA dosing

As reported in drug prescribing references, the standard dose of H2RA was defined as 300 mg/day of ranitidine, or 40 mg/day of famotidine (Table 1) [2–5]. A low H2RA dose was defined as 150 mg/day of ranitidine, or 20 mg/day of famotidine.

2.5. Outcomes

As most reported H2RA-related altered mental status occurs within the first few weeks of drug initiation, we followed all individuals for 30 days after the index date for two pre-specified outcomes [10–13]. Our primary outcome was hospitalization with evidence of an urgent head computed tomography (CT) scan — a proxy measure for delirium. We used an urgent head CT scan as a proxy for the presence of acute altered mental status for several reasons: (i) in the setting of altered mental status and the absence of an obvious drug toxidrome, metabolic disturbance or source of infection, neuroimaging is considered necessary to rule out intracranial etiologies by many popular clinical references; [28,29] (ii) based on prospective studies of common clinical practice, neuroimaging is commonly utilized in the routine evaluation of acutely confused older adults, even among those without focal neurologic findings or