Fall risk associated with the use of H2 antagonists in older persons

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Abstract

Background The previously reported association between the use of proton pump inhibitors (PPI) and hip fracture may either be due to decreased bone density or to increased risk of falling.

Objective To describe the association of the use of drugs for treatment of acid induced gastrointestinal complaints, PPIs and H2 receptor antagonists (H2RA) with the risk of becoming a recurrent faller, number of falls and with (hip)fracture rate and heel bone density in older persons.

Study design A prospective observational study with fall follow-up for one year and fracture follow up for six years.

Setting 11 municipalities in three areas of The Netherlands.

Participants A random sample of 1509 men and women aged 65 years and over who participated in the Longitudinal Aging Study Amsterdam.

Main outcome measures Time to the second fall within six months during a one year follow-up period. All fractures and hip fractures during a six year follow-up period. Broadband ultrasound attenuation (BUA) of the calcaneus on both sides.

Results The use of PPI was not associated with an increased risk of recurrent falls nor with fall rate. The use of H2RA yielded a significant rate ratio (RR) for ≥1 and ≥3 falls: RR 1.40, 95% confidence interval (CI) 1.02-1.92 and RR 2.19, CI 1.07-4.50, respectively when correction for age, sex, alcohol use and number of chronic diseases was applied. No significant associations between PPI or H2RA use and heel bone BUA was demonstrated.

The use of PPI or H2RA was not significantly associated with any fracture.

Conclusion The use of H2RAs, but not of PPIs is significantly associated with increased risk of falls.

Introduction

Falls and fall related complications are a major problem in the older population. One third of the older population experiences at least one fall each year and fifteen percent falls two times or more each year. Ten percent of falls leads to serious consequences resulting in medical treatment. Hip fracture occurs in 1-2 % of falls in older persons.[1 2 3] Hip fracture is associated with increased morbidity, institutionalisation rate, healthcare costs and mortality.[4 5]

Previous research has shown that several types of medication, mainly several psychopharmacological agents like benzodiazepines and tricyclic antidepressants are associated with increased fall risk.[6] Yang et al. reported an increased risk of hip fractures in persons of 50 years and older using proton pump inhibitors (PPI).[7] The authors hypothesised that decreased calcium solubility and intestinal malabsorption of calcium secondary to acid suppressive therapy may explain this association. The use of H2 receptor antagonists (H2RA), the most important alternative drugs for treatment of acid induced gastrointestinal complaints, was not associated with increased risk of hip fracture. In a study of Khalili et al. these findings were confirmed; particularly in women with a history of smoking, the use of PPI increased the risk of hip fracture.[8] In a large cohort study of Fraser et al. PPI use was also associated with non-traumatic fractures even when adjustments for multiple confounders, including bone mineral density (BMD) was applied.[9] In the Women's Health Initiative study the association with hip fracture was not found, but a modest association of PPI use with other fractures and with BMD of the hip.[10] Another large observational cohort study did not demonstrate relevant associations with fractures or accelerated BMD loss.[11] In a systematic review based on 10 observational studies the modestly increased risk of hip and vertebral fractures was confirmed but the authors concluded that there was significant statistical and clinical heterogeneity among studies.[12] Prospective data on falls were available in none of these studies. However in most of these studies an increased fall risk could be an alternative explanation of the reported association between the use of PPIs and hip and other fracture. In case of confounding by indication, this association should also exist for the use of H2RAs.

We performed an analyses of the association between the use of the 2 classes of antacids and fall risk. These possible associations were studied with the data available from the Longitudinal Aging Study Amsterdam (LASA), a large cohort study based on a sample of older men and women that is representative of the senior sector of the Dutch population. In addition to prospective falls and fracture

data, heel bone ultrasound reflecting bone mass density was also measured in this study.

Materials and methods

Sample

Data for this study were collected in the context of the Longitudinal Aging Study Amsterdam (LASA), an ongoing interdisciplinary cohort study on predictors and consequences of changes in autonomy and well-being in the aging population in the Netherlands.[13] The sampling and data collection procedures have been described in detail elsewhere.[14] In brief, a sample of older men and women (aged 55–85 years), stratified by age and sex, was drawn from the population registries of 11 municipalities in three areas of The Netherlands. In total, 3107 subjects (response rate=62,3%) were enrolled in the baseline examination (1992/1993).
The present study was performed using a sub sample of the LASA cohort, including 1509 respondents who participated in the second data collection cycle of LASA (1995/1996) and were born in or before 1930 (aged 65 years and older as of January 1, 1996). A face-to-face interview and tests were performed at home. The interviews were conducted by intensively trained and supervised lay interviewers. All interviews were tape-recorded in order to monitor the quality of the data.[14]
Starting from the 1995/1996 data collection cycle a three-year follow-up on falls was conducted in 1418 participants (Figure 1).
Informed consent was obtained from all respondents, and the study was approved by the Medical Ethics Committee of the VUmc and conducted according to the principles of the Helsinki declaration.

Assessment of falls.

Participants were asked to record falls every week for three years on a 'fall calendar' and to mail the calendar page to the research institute at three month intervals.[15] The participants were contacted by telephone if they were unable to complete the calendar, if the calendar was not returned even after a reminder or if it was completed incorrectly. Proxies were contacted if participants were not able to respond.
A fall was defined as 'an unintentional change in position resulting in coming to rest at a lower level or on the ground'.[16] A 'recurrent faller' was defined as a person who fell at least twice within a 6-month period during the fall follow-up.[17 18]

Because medication use was only registered at the start of the three year intervals we used the fall data of the first year of follow-up following the medication assessment.

Assessment of fractures

During the first follow-up episode (1995/96–1998/99) fracture data were collected prospectively using a fracture calendar. Participants were instructed to complete a set of questions regarding fractures every three months and send the data to our institute. In the second follow-up episode (1998/99–2001/02), fractures were retrospectively recorded during an interview at the end of the three-year period. If a participant died, their general practitioner or caregiver was contacted to supply information on whether a fracture had occurred since the last interview contact. More than 90% of the fractures included in the analyses could be verified with the general practitioner or hospital.[19]

Assessment of Quantitative Ultrasound Measurements.

Quantitative ultrasound data were obtained using the CUBA Clinical instrument (McCue Ultrasonics, Winchester, UK). Broadband ultrasound attenuation (BUA) (dB/MHz) was measured twice in both the right and left calcaneus. Mean BUA values were calculated from these four measurements. The short-term precision of BUA was reported as coefficient of variation (CV) of 3.4%, and long-term precision of BUA was reported as CV of 4.9%.[20 21] In a separate study, mean BUA of the calcaneus corrected for body weight yielded a correlation of 0.59-0.71 with bone mineral density (BMD) measurements of the lumbar spine, femoral neck, trochanter and total body assessed by dual-energy X-ray absorptiometry (DEXA).[22]

Assessment of medication use and co-morbidity

During the home visit the participants were asked to show to the interviewer all the medication that they regularly used. The names of all medications were recorded directly from the container. For each separate type of medication, the dosage, times a day and duration of use were recorded. In the database all medications were classified according to the ATC (Anatomical Therapeutical Chemical) coding system.[23]

During the interview the presence of several chronic conditions and alcohol use was assessed. The self-reported diseases were confirmed with the general practitioners' information.[24]

Statistical analysis

The association between chronic use of H2RAs or PPIs and time to becoming a recurrent faller, any fracture or hip fracture was examined by means of Cox regression analysis. The association between the use of H2RA or PPI and the number of falls within 1 year was calculated using binomial regression analysis. Chronic use of H2RAs or PPIs was defined by daily use for 1 year or more prior to the start of the fall follow-up. The association between the use of H2RAs or PPIs and mean BUA was examined with linear regression analysis. The analyses were adjusted for age, gender, alcohol use and number of co-morbid conditions. BUA results were additionally corrected for body weight. All analyses of falls were performed for one year fall follow-up, fracture follow-up was 6 years.
The analyses were performed using IBM SPSS Statistics version 19.0.0.

Results

The baseline sample consisted of 1509 participants with a mean age of 76.0 years (range: 64.8 to 88.8), 51.8% were female and 88 (5.8 %) lived in an institution. 361 (23.9%) of the participants used no medication. The other 1148 participants used a number of different medications ranging from 1 to 14. The mean number of medications used by all the participants was 1.89 per participant. H2 receptor antagonists (H2RA) were used by 76 and proton pump inhibitors (PPI) by 41 participants (table 1). One participant used 2 kinds of H2RAs. H2RAs and PPIs were used chronically by 52 and 29 participants respectively.
The number of participants who fell at least once within one year of fall follow-up was 468 (31.0%), 174 (11.5%) of them fell two or more times within one year. In the six years following the baseline medical interview 132 (8.7%) of the 1509 participants suffered a fracture. Hip fracture was registered in 39 of these fractures.

Medication, falls, bone density and fractures

Chronic use of PPIs was not associated with an increased risk of recurrent falls. Chronic use of H2RAs yielded a significantly increased rate ratio (RR) for ≥1 falls in 1 year: RR 1.40, 95% confidence interval (CI) 1.02-1.92 (p=0.04) adjusted for age, gender, chronic diseases and alcohol use. The association of chronic H2RA use and ≥2 falls year was not significant but for ≥3 falls again yielded a significant RR: 2.19, 95%CI, 1.07-4.50, p=0.03. (table 2) Chronic PPI use did not result in significant associations with any number of falls.

Although any use of H2RAs was associated with an increased risk of becoming a recurrent faller within 1 year (HR 1,73, 95%CI 1,00 - 2,99, p=0.05) , adjustment for age, gender, chronic diseases and alcohol use rendered this association non-significant. Selection of chronic H2RA users also rendered this association non-significant. (table 3)
No significant associations between PPI or H2RA use and heel bone BUA could be demonstrated.
The use of PPIs or H2RAs was not significantly associated with any fracture. Correction for age, gender, alcohol use and number of chronic diseases did not substantially change the levels of significance. (table 4)

Discussion

The hypothesis that PPI use might be associated with increased fall risk, thus increasing the risk of hip fracture, was not confirmed by our findings. On the other hand, the use of H2RAs, the alternative drugs for treatment of acid induced gastrointestinal complaints, was significantly associated with increased fall risk. This is an alarming finding because H2RAs are widely available, recommended and used as both prescription and non-prescription medication for mild heartburn and regurgitation.[25 26] This means that older persons with an already elevated fall risk could further increase this risk by using H2RA without their primary care physicians being aware of this.
The pharmacodynamical mechanism of this association is possibly to be found in the anticholinergic activity of H2RAs. Ranitidine and cimetidine are known to have low grade anticholinergic properties that probably gain in clinical significance with increasing age and vulnerability.[27; 28] Anticholinergic effects, both reflected by serum anticholinergic activity and by anticholinergic drug burden have been demonstrated to have detrimental effects on cognitive functions.[29; 30] The use of H2RAs is associated with cognitive impairment in community dwelling old persons.[31] The association between cognitive impairment, gait disorders and falls has been well established.[32;33;34] Furthermore, anticholinergic side effects are associated with slowing of both gait speed and response time and with falls.[35; 36]
The association between the use of PPIs and hip fractures could not be confirmed in our study. The uncorrected association between PPIs and heel bone ultrasound almost met the standards for significance. When correction for relevant confounders was applied no association was found. These findings are in accordance with the findings of Kaye and Jick who argued that the previously reported association between PPIs and hip fractures was the result of incomplete

correction for risk factors for osteoporosis.[37] In our study however, the number of fractures was low and the confidence intervals of both HR for fractures and regression coefficients for BUA were too wide to be able to draw conclusions from these findings.

The strength of our study is the combined availability of prospective fall data, heel bone ultrasound, fracture data and medication data. Because very detailed data could be obtained, we were able to correct for several relevant confounders. The relatively small number of H2RA and PPI users in this study (77 and 41, respectively) led to wide 95%-confidence intervals for the rate ratios for fall rate reflecting the amount of uncertainty concerning this outcome. Although we could not adjust for co-medication we did adjust for co-morbid conditions which, through adherence to nation-wide primary care treatment protocols probably led to indirect adjustment for the majority of co-medication that was used. Furthermore was our study sample size not large enough to allow for a reliable analysis of fracture rates in the subgroups of PPI and H2RA users. We therefore cannot rule out nor confirm an association of the use of these drugs with (hip) fractures. A modest association between PPI use and hip and vertebral fractures is however demonstrated in a review and meta-analysis of 10 observational studies.[12]

In a large case-control study of hip fracture risk in both PPI and H2RA users an increased risk for both drug classes was found.[38] Although the authors argue that this finding is probably the result of acid inhibition leading to decreased calcium uptake, increased fall risk might be an alternative explanation for the association of H2RA use with hip fractures.

In conclusion, our study demonstrates that H2RA use is associated with an increased fall rate whereas PPI use is not associated with fall rate nor fall risk. Ideally our findings should be confirmed in a randomised controlled trial or a large case-control study. However, such a study will probably never be performed because the “over the counter”(OTC) status of ranitidine has taken away (commercial) incentives to sponsor such a study. Therefore we foresee that more robust data on the fall risk increasing properties of H2RAs will be lacking in the near future. Although in our study, the rate ratio for 3 or more falls of H2RA use is only 2.19 with a wide 95%-confidence interval, these drugs are so widely used that the population attributable risk of even a slight increase of the number of frequent falls in older persons who use H2RAs is huge. We advise not to wait for confirmation of our results and to add a warning of potentially increased fall risk to the package insert of H2RAs. Especially older persons with mobility disorders or otherwise at high risk of falls should be encouraged to discuss the safety of the use of H2RAs with their primary care physician prior to initiating this therapy.

Figure 1. Flow diagram of study sample

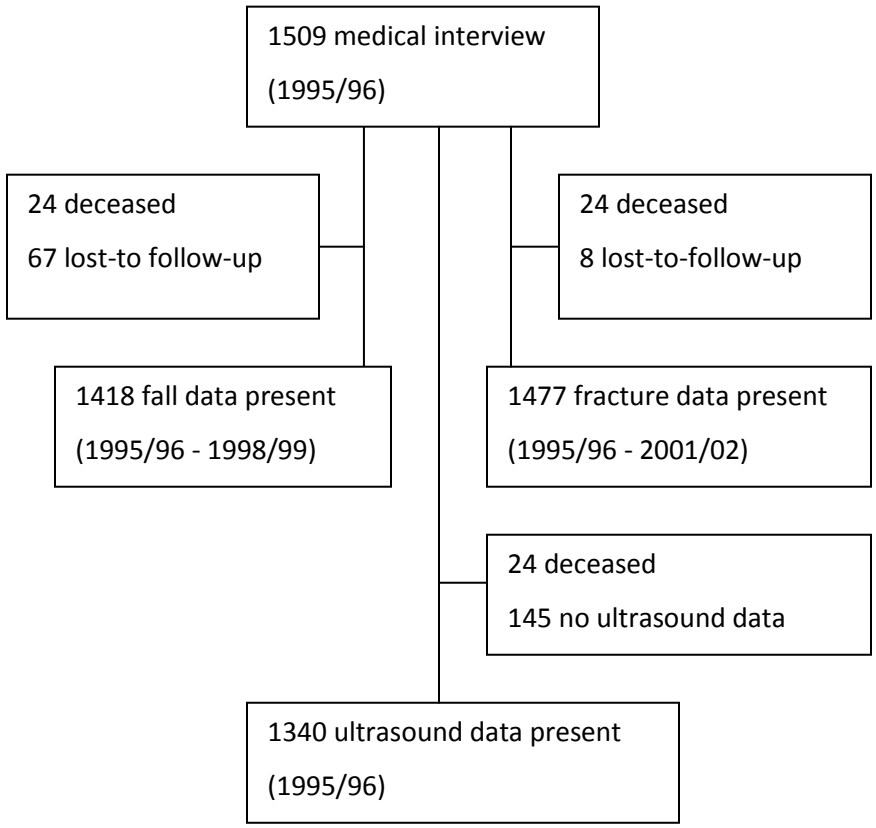

Table 1. Number of users per generic drug (n=1509)

	Number of users (%)
H2 receptor antagonists	
Cimetidine	21 (1.4)
Famotidine	8 (0.5)
Ranitidine	48 (3.2)
P**roton pump inhibitors**	
Omeprazol	41 (2.7)

Table 2. Chronic use of PPI or H2RA; associations with fall rate

	RR[a] ≥ 1 fall	95% CI	p	RR ≥ 2 falls	95% CI	p	RR ≥ 3 falls	95% CI	p
PPI	1.27	0.83-2.00	0.27	0.95	0.33-2.77	0.93	1.13	0.29-4.34	0.86
H2RA	1.40	1.02-1.92	0.04	1.47	0.80-2.71	0.21	2.19	1.07-4.50	0.03

[a] Rate ratio: all values adjusted for age, gender, number of chronic conditions and alcohol use

Table 3. Chronic use of PPI or H2RA; associations with risk of becoming a recurrent faller.

	HR[a]	95% CI	p
Proton pump inhibitor	0.93	0.30-2.92	0.90
H2 receptor antagonist	1.57	0.80-3.01	0.19

[a] Hazard ratio: all values adjusted for age, gender, number of chronic conditions and alcohol use

Table 4. PPI and H2RA; associations with 6 year fracture follow-up and with BUA

	Any fracture HR[a]	95% CI	p	Hip fracture HR[a]	95% CI	p	BUA Regression coefficient[b]	95% CI	p
PPI[c]	1.98	0.72-5.41	0.18	2.08	0.48-8.96	0.33	-4.00	-15.24 – 7.25	0.49
H2RA[c]	1.71	0.79-3.69	0.17	0.93	0.22-4.02	0.98	-2.33	-10.42 - 5.75	0.57

[a] Hazard ratio: correction for age, gender, number of chronic conditions and alcohol use

[b] correction for age, gender, number of chronic conditions, alcohol use and body weight

[c] BUA for PPI and H2RA use daily for 1 year or more.

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