ORIGINAL ARTICLE
eISSN: 2383-5699
Korean J Clin Geri 2016;17(1):22-28
https://doi.org/10.15656/kjcg.2016.17.1.22

노인에서 에스오메프라졸과 폐렴 간의 관계

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The Association between Esomeprazole and Pneumonia in the Elderly

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Background: Proton pump inhibitors (PPIs) are widely and routinely used to treat gastric acid-related disorders, such as gastroesophageal reflux disease (GERD) and peptic ulcer disease, in both inpatient and outpatient settings. Moreover, due to the characteristics of the elderly, GERD is one of common geriatric diseases, and then PPIs could be prescribed more frequently and longer in the elderly. Thus, in this study, the association between esomeprazole use and the prevalence of pneumonia has been evaluated in the elderly.

Methods: From the National Health Insurance Service-National Sample Cohort database of Korea from 2007 to 2010, the elderly were selected and separated into subgroups according to the gender (female vs. male) and GERD (GERD vs. non-GERD). Also, esomeprazole was divided into two groups according to the daily dose; <40 mg and ≥40 mg. Then, the subjects were subdivided according to the duration of esomeprazole treatment; 1 week, 2 weeks, 3 weeks, 30 days and ≥31 days. Logistic regression was also performed to identify the association between duration of esomeprazole administration and pneumonia.

Results: The total of 4,091 elderly subjects were selected. However, the association between the use of esomeprazole and the prevalence of pneumonia had been failed to show a significant association (in <40 mg esomeprazole group P=0.698, 0.504, 0.961 and 0.682 respectively; in ≥40 mg esomeprazole group, P=0.348, 0.846, 0.01and 0.713 respectively)

Conclusion: The esomeprazole use was not associated with the prevalence of pneumonia in the elderly.

Key Words: Proton pump inhibitor, Pneumonia, Esomeprazole, Gastroesophageal reflux disease, The elderly

INTRODUCTION

Proton pump inhibitors (PPIs) are widely and routinely used to treat gastric acid-related disorders, such as gastroesophageal reflux disease (GERD) and peptic ulcer disease, in both inpatient and outpatient settings. Also, GERD is considered as one of common geriatric diseases, owing to the abnormal peristalsis of the esophagus and dysfunctional

Received: April 30, 2016 Revised: May 28, 2016 Accepted: May 29, 2016.

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production of saliva in the elderly, which in turn makes esophageal mucosa vulnerable to the any damage. Thus, PPIs are more frequently used in the elderly.[1] However, there are considerable debates on the PPIs safety, especially on the long term use of PPIs due to the efficacy and tolerability of them. Some study reported that PPIs have inappropriately prescribed and overused in 50～60% of the hospitalized patients.[2,3]

Especially, there are numerous studies that have found a significant association between PPIs and pneumonia.[4-10] One study found that patients who were current users of PPIs (duration <30 days or high dose) had a significant association with community-acquired pneumonia (CAP).[8] The association between PPIs and pneumonia has been hypothesized that the increased gastric pH due to the PPI use may facilitate the growth of several bacteria in stomach, where it would be sterile with the normal pH of the stomach.[7] Moreover, this increase in bacteria can lead to pneumonia through microaspiration and lung colonization of them.[11]

However, two meta-analyses[12,13] and another observational study[14] have shown no significant association between PPI use and pneumonia, which, in turn, led to have questions about the link. Recently, Estborn et. al have also found that the occurrence of respiratory tract infections of patients receiving esomeprazole was similar to that of those receiving placebo.[15]

Therefore, considering the circumstance that the elderly can be taking many kinds of medication and longer than needed, this study was aimed to analyze this controversial relationship between CAP and PPIs, especially esomeprazole in those who were over 65 years old, with or without GERD by using the National Health Insurance Service-National Sample Cohort database of Korea from 2007 to 2010.

MATERIALS AND METHODS

In South Korea, all the Koreans are given a unique identification numbers and all the nationals are obligated to enroll in the Korean National Health Insurance Service (KNHIS). With this circumstance, the Korean government can collect national wide health information and can release representative random subject data, which is so called National Sample Cohort database. Further, the KNHIS uses the Korean Classification of Diseases (KCD), which is a similar system to the International Classification of Diseases 10 (ICD-10).

In the National Health Insurance Service-National Sample Cohort database of Korea from 2007 to 2010, the subjects those who had been treated with esomeprazole at least once from 2007 to 2010 were included. The exclusion criteria were as follows: 1) those who were less than 20 years old; 2) repeated esomeprazole users from 2007 to 2010; 3) subjects were enrolled after December in 2010. And then, more focus was given to those who were over 65 years old to see the association between esomeprazole use and CAP.

The definition of Pneumonia and gastroesophageal reflux disease (GERD) were based on Korean Classification Disease 6 (KCD 6; KCD code J09～18.9, J20～J22 and J40～J42 for pneumonia; KCD code K21.0 and K21.9 for GERD). Esomeprazole were restricted to oral agents as pneumonia were to community-acquired pneumonia in the outpatient setting. The analysis was done with the important operational definition: pneumonia was limited to the first occurrence after taking esomeprazole over 180 days. Then, the subjects were subdivided according to the duration of esomeprazole treatment as follows: 1 week (reference group for logistic regression), 2 weeks, 3 weeks, 30 days, and more than 31 days. When subdivided, 30 days of interval between administrations was considered a new set point to count.

The subjects were separated into subgroups according to the gender (female vs. male), and GERD (GERD vs. non-GERD). Also esomeprazole was divided into two groups according to the daily dose; <40 mg and ≥40 mg.

1. Statistical analysis

Mann-Whitney U-test was used to examine the association between the total dose of administrated esomeprazole and the prevalence of pneumonia. Logistic regression was also performed to identify the association between esomeprazole use and pneumonia. (between duration of esomeprazole

administration and pneumonia). All Statistical analyses were done by using SAS software, version 9.4 (SAS Institute, Inc., Cary, NC, USA).

RESULTS

1. Subjects

Among the subjects those who had been treated with esomeprazole at least once from 2007 to 2010 (n=4,022,086) those who were less than 20 years old were excluded (n=3,074,388) and among them, those who had gotten administered with esomeprazole for the first time were counted (n=26,652) and overlapping subjects were excluded (n=23,067). Also, the cases where subjects were enrolled after December in 2010 were all excluded (n=22,163). Finally, the cases in which daily dose frequency was 0 in 20 mg of esomeprazole (n=3) and the case in which daily dose frequency was 4 in 40 mg of esomeprazole (n=1) were eliminated (n=22,159). Then, finally were selected the main subjects who were over 65 years old (n=4,091).

2. Analysis in the daily dose of <40 mg esomeprazole

In subgroup 1 (65≥age; female; non-GERD), the prevalence of pneumonia was not significantly associated with esomeprazole use (P=0.698). The OR for 2 weeks, 3 weeks, 30 days, and ≥30 days of administration were 0.865, 0.923, 0.664 and 1.648 respectively and none of them were found to be statistically significant (P=0.764, 0.888, 0.362 and 0.357 respectively) (Table 1).

In subgroup 2 (65≥age; female; GERD), the prevalence

Table 1. Subgroup analysis in the daily dose of <40 mg esomeprazole in the elderly

Duration	Non-pneumonia	Pneumonia	P value*	OR	95% CI	P value†
Subgroup 1 (65≥age; female; non-GERD)						
Total	345	47	0.698			
1 week	173 (87.37)	25 (12.63)			ref	
2 weeks	48 (88.89)	6 (11.11)		0.865	0.336～2.229	0.764
3 weeks	30 (88.24)	4 (11.76)		0.923	0.300～52.840	0.888
30 days	73 (91.25)	7 (8.75)		0.664	0.275～1.602	0.362
≥31 days	21 (80.77)	5 (19.23)		1.648	0.570～4.763	0.357
Subgroup 2 (65≥age; female; GERD)						
Total	739	100	0.504			
1 week	340 (89.01)	42 (10.99)			ref	
2 weeks	157 (87.71)	22 (12.29)		1.134	0.655～1.965	0.653
3 weeks	56 (86.15)	9 (13.85)		1.301	0.600～2.820	0.505
30 days	149 (89.22)	18 (10.78)		0.978	0.545～1.755	0.940
≥31 days	37 (80.43)	9 (19.57)		1.969	0.888～4.364	0.095
Subgroup 3 (65≥age; male; non-GERD)						
Total	201	36	0.961			
1 week	85 (85.86)	14 (14.14)		ref		
2 weeks	37 (86.05)	6 (13.95)		0.985	0.351～2.761	0.976
3 weeks	15 (83.33)	3 (16.67)		1.214	0.311～4.743	0.78
30 days	44 (84.62)	8 (15.38)		1.104	0.430～2.831	0.837
≥31 days	20 (80)	5 (20)		1.519	0.490～4.707	0.469
Subgroup 4 (65≥age; male; GERD)						
Total	478	97	0.682			
1 week	193 (80.75)	46 (19.25)		ref		
2 weeks	115 (83.33)	23 (16.67)		0.839	0.484～1.456	0.533
3 weeks	45 (86.54)	7 (13.46)		0.653	0.277～1.541	0.330
30 days	96 (86.49)	15 (13.51)		0.656	0.348～1.234	0.191
≥31 days	29 (82.86)	6 (17.14)		0.868	0.340～2.213	0.767

GERD: Gastroesophageal reflux disease. *Mann-Whitney U-test. †Logistic regression.

of pneumonia was not significantly associated with esomeprazole use (P=0.504). The OR for 2 weeks, 3 weeks, 30 days, and ≥30 days of administration were 1.134, 1.301, 0.978 and 1.969 respectively and none of them were found to be statistically significant (P=0.653, 0.505, 0.940 and 0.095 respectively).

In subgroup 3 (65≥age; male; non-GERD), the prevalence of pneumonia was not significantly associated with esomeprazole use (P=0.961). The OR for 2 weeks, 3 weeks, 30 days, and ≥30 days of administration were 0.985, 1.214, 1.104 and 1.519 respectively and none of them were found to be statistically significant (P=0.976, 0.78, 0.837 and 0.469 respectively).

In subgroup 4 (65≥age; male; GERD), the prevalence of pneumonia was not significantly associated with esomeprazole use (P=0.682). The OR for 2 weeks, 3 weeks, 30 days, and ≥30 days of administration were 0.839, 0.653, 0.656 and 0.868 respectively. None of them were found to be statistically significant (P=0.533, 0.330, 0.191 and 0.767 respectively).

3. Analysis in the daily dose of ≥40 mg esomeprazole

In subgroup 1 (65≥age; female; non-GERD), the prevalence of pneumonia was not significantly associated with esomeprazole use (P=0.348). The OR for 2 weeks, 3 weeks, 30 days, and ≥30 days of administration were 1.758, 1.412, 1.537 and <0.001 respectively and none of them were found to be statistically significant (P=0.261, 0.615, 0.331 and 0.978 respectively) (Table 2).

In subgroup 2 (65≥age; female; GERD), the prevalence of pneumonia was not significantly associated with esome-

Table 2. Subgroup analysis in the daily dose of ≥ 40 mg esomeprazole in the elderly

Duration	Non-pneumonia	Pneumonia	P value*	OR	95% CI	P value†
Subgroup 1 (65≥age; female; non-GERD)						
Total	224	35	0.348			
1 week	113 (88.28)	15 (11.72)		ref		
2 weeks	30 (81.08)	7 (18.92)		1.758	0.658～4.699	0.261
3 weeks	16 (84.21)	3 (15.79)		1.412	0.368～5.425	0.615
30 days	49 (83.05)	10 (16.95)		1.537	0.646～3.661	0.331
≥31 days	16 (100)	0 (0)		<0.001	<0.001～>999.99	0.978
Subgroup 2 (65≥age; female; GERD)						
Total	736	112	0.846			
1 week	228 (87.36)	33 (12.64)			ref	
2 weeks	203 (86.75)	31 (13.25)		1.055	0.624～1.784	0.842
3 weeks	54 (83.08)	11 (16.92)		1.408	0.669～2.963	0.368
30 days	205 (86.5)	32 (13.5)		1.078	0.640～1.817	0.776
≥31 days	46 (90.2)	5 (9.8)		0.751	0.279～2.027	0.573
Subgroup 3 (65≥age; male; non-GERD)						
Total	224	30	0.01			
1 week	102 (89.47)	12 (10.53)			ref	
2 weeks	50 (89.29)	6 (10.71)		1.02	0.362～2.876	0.970
3 weeks	16 (66.67)	8 (33.33)		4.25	1.505～12.004	0.006
30 days	40 (90.91)	4 (9.09)		0.85	0.259～2.792	0.789
≥31 days	16 (100)	0 (0)		<0.001	<0.001～>999.99	0.968
Subgroup 4 (65≥age; male; GERD)						
Total	602	85	0.713			
1 week	170 (86.29)	27 (13.71)			ref	
2 weeks	150 (88.76)	19 (11.24)		0.798	0.426～1.492	0.479
3 weeks	50 (83.33)	10 (16.67)		1.259	0.571～2.778	0.568
30 days	192 (88.48)	25 (11.52)		0.82	0.458～1.467	0.503
≥31 days	40 (90.91)	4 (9.09)		0.63	0.209～1.901	0.412

GERD: Gastroesophageal reflux disease. *Mann-Whitney U-test. †Logistic regression.

Table 3. The total amount of esomeprazole administration and the prevalence of pneumonia

	Non-pneumonia (n=20,013)	Pneumonia (n=2,146)	P value*	OR	95% CI	P value†	AUC	Cut-off point (mg)
Total dose (mg)								
Median (min~max)	280 (20~6720)	280 (20~2600)	<0.001	0.998	0.997~0.999	<0.001	0.524	240

*Mann-Whitney U-test. †Logistic regression Subjects were over 20 years old.

prazole use (P=0.846). The OR for 2 weeks, 3 weeks, 30 days, and ≥30 days of administration were 1.055, 1.408, 1.078 and 0.751 respectively and none of them were found to be statistically significant (P=0.842, 0.368, 0.776 and 0.573 respectively).

In subgroup 3 (65≥age; male; non-GERD), the prevalence of pneumonia was significantly associated with esomeprazole use (P=0.01). The OR for 2 weeks, 3 weeks, 30 days, and ≥30 days of administration were 1.02, 4.25, 0.85 and <0.001 respectively. Among them, 2 weeks of administration was found to be statistically significant (P=0.006).

In subgroup 4 (65≥age; male; GERD), the prevalence of pneumonia was not significantly associated with esomeprazole use (P=0.682). The OR for 2 weeks, 3 weeks, 30 days, and ≥30 days of administration were 0.798, 1.259, 0.82 and 0.63 respectively and none of them were found to be statistically significant (P=0.479, 0.568, 0.503 and 0.412 respectively).

4. The association between esomeprazole in total dose and the prevalence of pneumonia

The prevalence of pneumonia was significantly decreased as the total dose of administrated esomeprazole was increased (Table 3). The odds ratio (OR) was 0.998 with 95% Cl (0.997~0.999) and statistically significant in both Mann-Whitney U-test and logistic regression (P<0.001 both).

DISCUSSION

Besides of the common adverse effects including headache, nausea, abdominal pain and diarrhea,[16,17] the use of PPIs has been associated with serval rare adverse effects, such as, vitamin B12 deficiency,[18-22] iron deficiency.[23,24] In this study, the association between esomeprazole use and CAP was analyzed by using the National Health Insurance Service-National Sample Cohort database of Korea from 2007 to 2010.

As shown Table 1 and 2, the subjects were subdivided by the daily dose of esomeprazole (<40 mg vs. ≥40 mg) and the duration of esomeprazole treatment (1 week, 2 weeks, 3 weeks, 30 days and ≥31 days) over 65 years old. As a result, the association between the use of esomeprazole and the prevalence of CAP had been failed to have a significant association. The result seemed to be contrary to the above hypothetical mechanism of pneumonia due to PPI use in other studies. However, one population-based case-control study reports that there is not any association between use of PPIs and the increased pneumonia risk and concludes that the observed increased risk in some study may be due to confounding.[14] Jena et al. have also reported that the association between the PPI use and CAP would be confounded and have assessed for that by using the 'falsification approach'.[25] The results of the study showed that similar associations with pneumonia were found in chest pain and urinary tract infection. This suggests that although the PPI use and pneumonia appears to have a significant association statistically, this could be confounded in reality.

In this study, only male patients who took ≥40 mg of esomeprazole daily, were ≥65 years old and did not have GERD showed statistically significant association with pneumonia with high OR of 3 weeks (OR: 4.25; 95% Cl: 1.505~12.004) (Table 2). However, only 3 weeks of duration turned out to be statistically significant while others not. Thus, without controlling the possible confounding factors, this result can be not interpreted as the meaningful outcome. Moreover, GERD was considered as the confounding factor, but the results showed that GERD was not any sig-

nificant factor. Thus, more compact variables be necessary in the future study.

In addition, Giuliano et al.[8] reports that those who receiving PPIs, particularly <30 days, showed increased risk of CAP. Thus, to examine if there was any the association between the total amount of esomeprazole use and CAP, the Mann-Whitney U-test and logistic regression were done in ages of 20 years and over. If CAP was dose-specific to the PPIs, there might be cut-off point, to which the risk of CAP would be increased and after which decreased. Table 3 showed the statistically significant negative association between esomeprazole in total dose and the prevalence of pneumonia over 20 years old. (OR: 0.998; 95% Cl: 0.997～0.999). However, the OR (0.998) and AUC (0.524) could suggest that the association would be weak, possibly not significant in reality, because the numbers indicates that the probability of correctly estimating the right pneumonia cases with this cut-off point indicates that almost 52%, which does not have enough power to evaluate the association between use of esomeprazole and the prevalence of pneumonia in this study. Thus, it could not be said that esomeprazole use and CAP were on negative association based on this result even though it appeared statistically significant. This negative tendency could be also explained by the possible bias from the huge number of participants being analyzed.

Despite of the huge sample size, the major limitations of this study were the lack of demographic and health characteristics of subjects - so the effects of any differences such as diabetes, chronic obstructive pulmonary disease, and smoking etc. in them could not be analyzed, which would hopefully be expected to give us the exponible confounding factors in the association - ; no true control groups such as those who had not taken any PPIs in each analyses, even though the 7 days of PPI use was considered a reference; and only esomeprazole has been included in this study. Thus, in future study, the true control group in which no PPIs and no H2 blockers are administered should be selected to compare and all the available PPIs should be included so as to better evaluate the relationship between PPI use and the risk of pneumonia.

Lastly, this study was the first to evaluate the PPIs use and the risk of CAP by using Korean National Sample Cohort database, but to fail to reveal any significant association between the esomeprazole use and the prevalence of pneumonia in the elderly.

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