Long-term Proton Pump Inhibitors induces recurrent Urinary Tract Infections: A case study

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Abstract. A 28 y.o. woman with dyspepsia had been taking proton pump inhibitor (PPI) for about seven months. After that, she experienced recurrent urinary tract infections (UTI), which she never experienced before. There was three episodes of UTI requiring antibiotic occurred, those are in January 2017, February 2017, and May 2017. During those episodes, she took once to twice daily dose of PPI regularly due to dyspepsia which she had experienced since July 2016. After stopping the PPI medication in August 2017, she had no single episodes of UTI (until June 2018). Based on patient prognosis in this case, there might be possibility that the patient developed recurrent UTI after long-term use of PPI. The mechanism is unclear but it seems that PPI induced hypomagnesemia, and then influences immune system, causing urinary tract infections.

Keywords: Dyspepsia, esomeprazole, hypomagnesemia, pantoprazole

1. Introduction
Proton pump inhibitors (PPI) is very commonly used to treat dyspepsia. PPI acts on gastric parietal cells, it binds to H+/K+-exchanging ATPase, inhibiting acid production. Some reports stated that long-term use of PPI is associated with increasing risk of pneumonia, clostridium infection, bone fracture, iron and B12 deficiency anemia [1, 2]. There might be a correlation between PPI and UTI (urinary tract infections). A retrospective analysis shows that two patients using PPI experienced UTI after 2 wk to 9 mo follow-up [3]. Some other cases might show the possibility of correlation [4, 5].

2. Case presentation
A 28 y.o. woman was visiting an internist physician in July 2016 with the complaints of dyspepsia, those were bloating, upper abdominal pain which was almost happened every day, and sometimes diarrhea in the morning. These symptoms had been happened for 3 wk. The patient was conducting self-treatment using esomeprazole 40 mg once daily combined with sucralfate 10 mL four times daily, 1 h before meal. However, the use of those medication did not improve patient’s dyspepsia symptoms. From the patient’s explanation, physician prescribed PPI (lansoprazole 30 mg twice daily) combined with domperidone 10 mg three times daily before meal. Again, the use of those medications for 1 wk did not improve patient’s symptoms. Therefore, physician recommended endoscopy for diagnosing. On July 14, 2016, endoscopy followed by biopsy procedures was done to take esophagus and gastric tissue sample. From the endoscopy result, it was concluded to be erosive esophagitis. From the biopsy of esophagus tissue, it was stated to be Barret’s Esophagus, while the biopsy of gastric tissues stated to be chronic gastritis, not active, non-atrophic, with intestinal metaplasia. Thus, based on Barret’s
Esophagus therapeutic management, patient was recommended to consume long-term PPI. Patient was recommended to consume lansoprazole 30 mg once daily before bed to undetermined time. Therefore, the patient then followed physician’s instruction to take lansoprazole 30 mg once daily before bed for 1 yr. In January 2017, 7 mo after using PPI, the patient developed first episode of UTI. A woman felt burning while urinate and blood presented in her urine, then rushed to the hospital and it was confirmed UTI (laboratory result can be seen below). The doctor prescribed cefixime 200 mg twice daily for 5 d, and 1 wk later after stopping antibiotic, the urine laboratory test showed improvement with normal findings. In February and May 2017, she experienced the second and third episode of UTI. For the second and third episode, again she felt burning while urinate with no blood seen in her urine, and the symptom was improved after using cefixime 200 mg twice daily for 5 d.

Table 1. Laboratory results of first episode of UTI.

| Laboratory parameter | 8 Jan 2017 (before using antibiotic) | 20 Jan 2017 (7 d after stopping antibiotic) | Normal value |
|----------------------|--------------------------------------|------------------------------------------|-------------|
| Color                | Red                                  | Yellow                                   | Yellow      |
| Clarity              | Cloudy                               | Slightly Cloudy                          | Clear       |
| Albumin (Protein)    | 300 mg dL⁻¹                          | Negative                                 | Negative    |
| pH                   | 6.0                                  | 7.0                                      | 4.6 to 8.0  |
| Sp. Gravity          | 1.020                                | 1.018                                    | 1.010 to 1.030 |
| Blood/Hb             | ≥ 250 μL⁻¹                           | Negative                                 | Negative    |
| Leucocyte Esterase   | 500 μL⁻¹                             | Negative                                 | Negative    |
| RBCs                 | Full                                 | Negative                                 | Negative    |
| WBCs                 | Full                                 | 0 to 2/HPF                               | 0 to 8/HPF  |
| Bacteria             | Positive 1                           | Negative                                 | Negative    |

On August 12, 2017; based on internist physician instruction, the second endoscopy procedure was done, and the result was normal condition of gastric and duodenum. The biopsy result was obtained 3 d afterwards giving the results of non-specific chronic esophagitis without Barret’s Esophagus. This patient case is quite interesting because Barret’s Esophagus has characteristic of being progressive, and the use of PPI was intended to prevent the progressiveness of Barret’s Esophagus. Based on the newest endoscopy and biopsy results, physician recommended the patient to stop PPI use, it was no longer needed and this is the reason the patient stopped consuming PPI. After stopping PPI, there was no episodes of UTI happened. This observation was made until June 2018, or nine months after stopping PPI.

Based on Naranjo scale, there is a probability of UTI adverse effect from using long-term PPI. The criteria of this probability are due to availability of previous conclusive report, adverse event appear after PPI was administered, the adverse reaction improve when the drug was discontinued, the adverse event confirmed by objective evidence, by this case is urine laboratory test in table 1 (total score of 5 to 8: probable) [6].

3. Discussion

From the above table and Naranjo scale, it is likely that the patient suffered from UTI. There was leucocyte, mass erythrocyte, albumin, and bacteria found in the urine. Unfortunately, for second and third episode, there was no laboratory test due to refusal from the patient, but from the symptom she experienced, it is also likely to be UTI, especially the symptom disappeared right after the patient took antibiotic to relieve the stinging pain while urinate.

There is another case presented that relate PPI to UTI. The patient suffered from recurrent UTI and hypomagnesemia while using PPI. Other causes of hypomagnesemia (i.e. vomiting, diarrhea, familial genetic related to hypomagnesemia, alcoholism, laxatives and diuretics medication history) were not found in the patient history [4]. Other similar case showed that omeprazole induced hypomagnesemia and the patient also suffering from UTI [5].
According to Torpey et al. [3] study, a presentation of UTI can be seen within 2 wk to 9 mo consuming PPI. The mechanism of how PPI increases the risk of recurrent UTI is unclear but it seems that PPI induced hypomagnesemia, and then influences immune system, by this case is urinary tract infection. Other studies show the significant correlation between PPI and hypomagnesemia [5, 7–10]. PPI alters the intestinal pH, this affects affinity reduction between TRPM6/7 and Mg$^{2+}$, thus reducing the absorption of Mg$^{2+}$, and this lead to hypomagnesemia [11]. Somehow hypomagnesemia is often correlated with urinary tract infections. Magnesium has a role in regulating immune system. In animal models, hypomagnesemia activates the inflammatory response, such as IL-6, TNF-α, macrophages, neutrophils, and endothelial cells. Hypomagnesemia also inhibiting the release of nitric oxide (NO) from cell, which has functions in preventing infections in body cavities, thus increasing the possibility of recurrent infections [12–14]. PPI induced hypomagnesemia is a rare but could lead to complications [11]. It is important to check the patient’s magnesium status before initiating long-term PPI.

4. Conclusion
This case shows that long-term use of PPI may increase the possibility of experiencing recurrent UTI. However, further and advanced investigations are needed to confirm it. Patient’s magnesium status before and after initiating long-term PPI should be checked regularly and the event of UTI can be investigated.

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