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EDITORIAL

Risk of pneumonia associated with proton pump inhibitor use

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Abbreviation
PPI   Proton pump inhibitor

Proton pump inhibitors (PPIs) are considered relatively safe and are frequently prescribed worldwide for treating acid-related upper gastrointestinal disorders and preventing peptic ulcers [1]. However, concerns regarding various PPI-related adverse effects have recently emerged. PPI-related adverse outcomes include enteric infection (e.g., *Clostridioides difficile* infection), fractures, and pneumonia [2–5].

The association between PPI use and pneumonia was first reported in 2004 [5], and has since been the subject of numerous studies. A meta-analysis revealed that a short duration of PPI use has been associated with a significant risk, whereas chronic PPI use has not [6]. Attention must be paid to the reverse causality (protopathic bias) that occurs when outcomes are associated with exposure resulting from early signs and symptoms of the outcome under investigation [7]. Regarding this bias, Othman et al. reported that the risk of pneumonia was higher before PPI prescription than after [8]; thus, the association between PPI use and the risk of pneumonia remains inconclusive. To date, most associations between PPI use and the risk of pneumonia have been attributed to confounding and protopathic biases [6, 8, 9].

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Several novel statistical methods have recently been proposed to address protopathic bias in studies on PPI-related adverse outcomes. Lo et al. introduced a modified lag-time approach to investigate the association between PPI use and mortality [10]. In this design, the PPI-exposure period was followed by a lag time (2–6 years) to rule out reverse causation, and mortality risk was estimated in the subsequent period.

Considering the pathogenic mechanisms, PPI-related adverse events can be divided into those associated with short-term (e.g., pneumonia and enteric infection) and chronic use (e.g., fractures). Therefore, simply excluding new users, even to control for protopathic bias, may not be an appropriate approach for investigating the association between PPI use and the risk of pneumonia.

Maret-Ouda et al. reported an association between PPI use and pneumonia using a relatively new technique called self-controlled case series analysis [11]. This design is well suited for investigating associations with acute and transient conditions (e.g., pneumonia), especially when the event does not affect subsequent exposures (e.g., PPI use) [12, 13]. This study investigated 519,152 participants including 307,709 PPI treatment periods in a population-based Swedish nationwide cohort. A self-controlled case series design was used to compare events during each participant's PPI-exposed and non-exposure periods. This design makes it possible to control for all time-invariant confounders, including unknown confounders.

Of note is the ingenuity in defining the PPI-exposure status. The PPI-exposure period was defined as the period from the date of PPI dispensation to 30 days after ending the treatment to allow for normalization of the gastrointestinal microbiome. The 60 days prior to the date of PPI dispensation was excluded from the unexposed period and

classified as the pre-exposure period. Overall, PPI use increased the risk of pneumonia by 73%. In contrast, histamine type-2 receptor antagonist use showed only an 8% increase in risk, supporting the specific effects of PPI use. Furthermore, PPI use increased the risk of pneumonia regardless of the duration of exposure, with the unexposed period as a reference (120–159% increase). Interestingly, the pre-exposure period was associated with a higher risk (264% increase) than the exposure period, implicating protopathic bias. The protopathic bias here potentially stems from misdiagnosing symptoms of preclinical stage pneumonia as gastroesophageal reflux disease leading to PPI use, and concomitant PPI use during pneumonia treatment and subsequent PPI exposure for a certain period after discharge. By classifying the periods in this manner and comparing the exposure periods with the baseline period, new PPI users were demonstrated to have an increased risk of pneumonia, even after ruling out protopathic bias. The definition of PPI-exposure status in this study makes sense for addressing protopathic bias, and the good statistical power associated with a large sample size provides compelling evidence.

In summary, when investigating PPI-related adverse outcomes, it is necessary to classify events into new and chronic use-related events according to the assumed mechanism and appropriately analyze them. In other words, when estimating the effects of chronic use, there is no problem using the modified lag-time approach. However, when estimating the effects of short-term use, appropriate methods, such as self-controlled case series analysis, should be used.

Declarations

Conflict of interest The author KI is an associate editor of the Journal of Gastroenterology. The remaining authors declare no conflict of interest for this article.

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