EDITORIAL

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Navigating the risks of using concomitant antipeptic agents in light of osteoporotic concerns

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Antipeptic medications, including proton pump inhibitors (PPIs) and H2-receptor antagonists (H2RAs), are among the most commonly prescribed drugs for gastrointestinal disorders worldwide [1]. These drugs reduce gastric acid production and play both a therapeutic and prophylactic role in the treatment of acid-related upper gastrointestinal disorders and the prevention of stress ulcers [2]. However, the long-term use of these drugs has raised significant concerns. Previous epidemiologic studies have mainly focused on the association of PPIs with major health problems. Documented adverse effects of PPIs include renal insufficiency, osteoporosis with subsequent fractures, fundic gland polyps, various bacterial infections (including pneumonia, spontaneous bacterial peritonitis, and *Clostridium difficile* infection), dementia, and a possible increased risk of mortality [2-4].

The association between the use of antipeptic agents, such as PPIs and H2RAs, and risk of osteoporotic fractures is one of major concern because of its significant implications regarding quality of life, mortality, and healthcare costs [5]. A meta-analysis of several observational studies showed an association between the use of PPIs and an increased risk of hip fractures as well as fractures at any site [6]. Conversely, few studies have focused on H2RAs or mucoprotective agents, and H2RAs are associated with lower, even negligible, risk for osteoporosis compared to PPIs [5,7].

The intricate relationship and causality between the administration of these agents and the occurrence of osteoporotic fractures is complex and incompletely understood. One potential mechanism under investigation suggests that suppression of gastric acid, a common action of both PPIs and H2RAs, may adversely affect the balance of bone remodeling. This process, which is essential for maintaining bone homeostasis, relies on a finely tuned balance between bone formation by osteoblasts and bone resorption by osteoclasts [8]. Moreover, impaired calcium absorption, a consequence of reduced gastric acidity from prolonged PPI and H2RA use, may tip this balance toward increased bone resorption, thereby accelerating the progression of osteoporosis [9].

Oh et al. [10] emphasized that the concomitant use of a PPI and H2RA increases the risk of osteoporosis-related fractures compared to the use of either agent alone. Thus, the authors recommend against their combined use. Conversely, they found that a combination of either a PPI or H2RA with mucoprotective agent is not associated with such risk compared to an acid suppressant alone. This conclusion is distinct from those of previous studies, which have primarily compared the risks associated with individual antipeptic agents, particularly between H2RAs and PPIs.

However, Oh et al. [10] also had inherent limitations related to the use of claims-based data and the observational nature of the study. A major limitation was the inability to fully account for all covariates, such as scenarios requiring long-term use of dual acid suppression therapies, which are associated with an increased risk of fracture and complex comorbidities that are not fully explained by the Charlson comorbidity index alone. This limitation raises concerns about potential bias. Other data-inherent limitations included the lack of detailed results of certain tests, such as bone mineral density, and uncertainties about adherence to prescribed medication regimens. Further limitations included the absence of a detailed analysis regarding the duration of use of H2RAs or mucoprotective agents and the lack of individual assessments of the association between antipeptic agents and specific fracture sites.

Despite these limitations, the study is notable for its eval-

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uation of the risk of osteoporotic fracture not only with the use of several individual antipeptic agents but also with their combined use. The clinical significance of the results lies particularly in the suggestion of an increased risk associated with the concomitant use of antipeptic medications. This finding adds a new dimension to our understanding of the potential impact of antipeptic agent prescription practices and highlights the need for caution when prescribing PPIs and H2RAs together. Furthermore, PPIs or H2RAs are commonly combined with mucoprotective agents in clinical practice. The study attempts to clarify the relationship between such combination therapy and the risk of osteoporotic fracture in the context of actual prescribing patterns. The findings prompt a reevaluation of current prescribing practice and underscore the importance of considering the cumulative effects of antipeptics on bone metabolism, further contributing to the ongoing discourse on the safe and effective management of acid-related gastrointestinal disorders.

There is a clear need for comprehensive studies to elucidate the mechanism between antipeptic agents and osteoporosis and well-structured cohort studies to validate these risks. Current evidence suggests that the use of antipeptic agents, especially over a prolonged period, should be approached with caution. It is essential to strike a balance between recognizing the potential risks and benefits of such medications, discouraging unnecessary prescriptions in favor of a more personalized treatment approach.

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