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Proton pump inhibitor: Is it a wolf in sheep's clothing?

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BASED ON ARTICLE

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SUMMARY

It is known that proton pump inhibitor (PPI) use may alter the gut microbiota or have a direct action on the immune system and lead to infections. However this theory is often debated but never convicingly proven. Lassalle et al assessed the associations between PPI use and serious infections in children, overall and by infection site and pathogen. The authors used the French Health Data System for the same. They included all children born 2010-18, who received a treatment for gastroesophageal reflux disease or other gastric acid–related disorders. They included PPIs, histamine 2 receptor antagonists, or antacids/alginate. The index date was defined as the first date any of these medications was dispensed. Children were followed up until admission to the hospital for serious infection, loss of follow-up, death. The exposure of interest was PPI use over time, as measured by PPI exposure status (categorized as unexposed or exposed), history of PPI exposure (none, past, ongoing), and duration of any ongoing PPI exposure (unexposed, ≤6 months, 7-12 months, >12 months). Treatment withdrawal was defined by a 90-day gap after the last day of exposure without any new PPI being dispensed. They applied a 30-day lag on exposure because of the latency in the development of infection and to limit protopathic bias (when a drug of interest is initiated to treat symptoms of the disease under study before it is diagnosed). Serious infections were classified by site (digestive tract; ear, nose, and throat [ENT]; lower respiratory tract; kidneys or urinary tract; skin; musculoskeletal system; and nervous system) and by pathogen, viral or bacterial. The study population comprised 1 262 424 children (median [IQR] follow-up, 3.8 [1.8-6.2] years), including 606 645 who received PPI (323 852 male [53.4%]; median [IQR] age at index date, 88 [44-282] days) and 655 779 who did not receive PPI (342 454 male [52.2%]; median [IQR] age, 82 [44-172] days). PPI exposure was associated with an increased risk of serious infections overall (aHR, 1.34; 95% CI, 1.32-1.36). Increased risks were also observed for infections in the digestive tract (aHR, 1.52; 95% CI, 1.48-1.55); ear, nose, and throat sphere (aHR, 1.47; 95% CI, 1.41-1.52); lower respiratory tract (aHR, 1.22; 95% CI, 1.19-1.25); kidneys or urinary tract (aHR, 1.20; 95% CI, 1.15-1.25); and nervous system (aHR, 1.31; 95% CI, 1.11-1.54) and for both bacterial (aHR, 1.56; 95% CI, 1.50-1.63) and viral infections (aHR, 1.30; 95% CI, 1.28-1.33). Authors concluded that PPI use was associated with increased risks of serious infections in young children. Proton pump inhibitors should not be used without a clear indication in this population [1].

COMMENTARY

The last sentence of the author's conclusion above is the most sensitive statement of the entire study. All this while we considered PPI as a harmless drug with negligible immediate side effects, the "sheep" of all drugs used in gastrointestinal practice. PPIs are known to directly affect multiple functions of the immune system, specifically neutrophil functions. Acid secretion by parietal cells is an important immunological barrier in the gastrointestinal tract, which is why hypochlorhydria induced by PPI increases the risk of bacterial colonization, alterations in intestinal flora and susceptibility to enteric infections. The composition of the microbiota undergoes major changes during infancy, especially in preterm infants. Therefore, PPI exposure during this period could have a notable impact. Studies in the past have demonstrated that intense suppression of gastric acid secretion is associated with increased risk of Clostridium difficile, non-typhoid Salmonella and Campylobacter infections [2,3] Pneumonia has been widely associated with PPI use, especially over the short term (usually fewer than 30-90 days). The most likely explanation for the increased risk of respiratory infections is that PPI-induced hypochlorhydria increases microaspiration of gastric contents, and the subsequently pneumonia [4]. Lasalle et al in this study have clearly shown that all systemic serious infections in young children are higher in those who are on PPI. Any chance of an argument with a protopathic effect was also eliminated [1]. There is also a growing concern that PPI may have other systemic side effects in adults (cardiovascular disease, dementia, increased fractures, higher complications in cirrhosis). Gastric cancers and neuroendocrine tumors are also linked with increase use of PPI [5].

However since all these side effects are occult and delayed, not much attention is paid to the same. Each physician prescribes without giving much thought, not worrying about the possible indirect harm. Crying and regurgitation are among the most common reasons why parents seek medical care for otherwise healthy infants. Pediatricians often prescribe PPI in this situation with the presumption of gastroesophageal reflux disease (GERD). It is often not differentiated for a physiological GER (happy spitters). They are compelled to use PPI especially in incessant mothers who worry about small volumes of reflux and over-report choking symptoms with the slightest growth faltering. Since GERD is difficult to document without pHmetry, the diagnosis in infants is empirical, mostly considered "benefit of doubt". Hence the overdiagnosis and over prescription of PPI. Children at high risk for GERD include those with medical complexity and serious, underlying chronic health conditions (eg, cerebral palsy) that frequently impair oromotor function and airway protection, esophageal motility and sphincter coordination.

What does this study teach us? As benign as PPIs may seem, the "big bad wolf" is actually on the prowl. Mindless prescriptions of PPI in office practice must be checked. The happy spitter today may return with a life threatening meningitis tomorrow. The drug should be stopped at the earliest in younger children and restarted only when the indication is justified or compelling. PPI should rather be reserved for high risk groups who deserve long- term therapy.

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