Indian Academy of Pediatrics (IAP)

nRICH

Newer **R**esearch and recommendations **I**n **C**hild **H**ealth

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UNDER THE AUSPICES OF THE IAP ACTION PLAN 2023

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Dear fellow IAPans,

nRICH

Newer **R**esearch and recommendations **I**n **C**hild **H**ealth-aims to bring you the abstracts of some of the breakthrough developments in pediatrics, carefully selected from reputed journals published worldwide.

Expert commentaries will evaluate the importance and relevance of the article and discuss its application in Indian settings. nRICH will cover all the different subspecialities of pediatrics from neonatology, gastroenterology, hematology, adolescent medicine, allergy and immunology, to urology, neurology,vaccinology etc. Each issue will begin with a concise abstract and will represent the main points and ideas found in the originals. It will then be followed by the thoughtful and erudite commentary of Indian experts from various subspecialties who will give an insight on way to read and analyze these articles.

I'm sure students, practitioners and all those interested in knowing about the latest research and recommendations in child health will be immensely benefitted by this endeavor which will be published online on every Monday.

Happy reading!

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Association Between Proton Pump Inhibitor Use and Risk of Asthma in Children

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BASED ON ARTICLE

Yun-Han Wang, Viktor Wintzell, Jonas F. Ludvigsson, Henrik Svanström, and Björn Pasternak. JAMA Pediatr. 2021 Apr; 175(4):1–10.

SUMMARY

The incidence of asthma is rising globally and is a major public health issue. One known causative factor in the pathogenesis of asthma is the disturbance in the human microbiome. Proton pump inhibitors (PPI's) are known to alter both gut and lung microbiota through inhibition of gastric acid secretion.

PPIs are the first-line therapy for acid-related gastrointestinal tract disorders in children. The use of PPI's both off-label and prolonged has increased substantially in paediatric practice, despite limited data supporting the safety of PPI.

There is available data, primarily derived from studies of drug use in pregnancy, suggesting that exposure to PPIs may be associated with subsequent development of asthma. One previous cohort study in infants, who were prescribed PPI's in the first six months of life reported a statistically significant increase in asthma. However whether PPI use in the broad paediatric population is associated with risk of asthma is not known.

The authors of the present study ,therefore aimed to investigate the association between PPI use among children and adolescents aged 0 to 17 years- and the risk of asthma by conducting a nationwide register-based cohort study in Sweden.

Their research question: "Is proton pump inhibitor (PPI) use associated with risk of asthma in children?"

Design of the study: The study data were captured from mandatory Swedish registers that cover nationwide health care and administrative records. The source population consisted of all children in Sweden who were younger than 18 years at some point from January 1, 2007, to June 30, 2016. From the source population, they identified all children who initiated PPI use. This was defined as patients prescribed their first PPI during the study period and who had no PPI prescription in the year prior. The PPI dispensing date served as the index date. PPIs included Omeprazole, Esomeprazole, Pantoprazole,

Lansoprazole, and Rabeprazole .

The cohort was established through a matching process, of selecting each child who initiated PPI to an appropriate comparator the same age who did not, and further matched on the basis of a Propensity score based on demographic, socioeconomic similarities, comorbidities, co-medications etc.

Patients with history of asthma (defined as a diagnosis of asthma within 5 years before the index date or a prescription for an asthma medication within 1.5 years before the index date) were excluded as also were children who had

interstitial lung disease, emphysema, bronchiectasis, lung cancer, chronic obstructive pulmonary disease, heart failure, bronchopulmonary dysplasia, congenital lung malformation, and primary immunodeficiency disease before the index date; pneumonia within 3 months before the index date; liver failure; and use of histamine 2 receptor antagonists (H2RAs) within 1 year before the index date.

Outcome : The primary outcome was incident asthma, defined as a first diagnosis of asthma (primary or secondary diagnosis) captured from hospital records and specialist outpatient care or 2 or more independent prescriptions for any asthma medication filled within 90 days.

Statistical Analysis: The final study cohort included 80 870 pairs of initiators and non-initiators of PPI use. They computed incidence rates and absolute risk difference in incidence with 95% CIs based on Poisson regression. This cohort was followed up from the day after the cohort entry date, till the end of the study period (December 31, 2016), or until a first asthma event or chronic obstructive pulmonary disease diagnosis, emigration, death (whichever came first). SABA (Short acting Inhaled Bronchodilators) were removed from the primary outcome definition, as these drugs are also prescribed for children to relieve transient wheezing or asthma like symptoms . Also patients who received anti H.pylori. treatment after PPI as well as those who later received H2 Receptor antagonists were excluded.

Results: In the primary analysis, the incidence rate of asthma was 21.8 per 1000 person-years among those who initiated PPI use and 14.0 per 1000 person-years among those who did not; **Thus, PPI use was seen to be associated with an increased risk of asthma**. (HR 1.57; 95% CI, 1.49-1.64) (HR i.e. Hazard Ratio >1 indicates a greater risk of this event, in this case development of Asthma)

To Sum Up:

In this nationwide cohort study, the authors observed a significant 57% increased risk of asthma among children who initiated PPI use compared with those who did not initiate PPI use. An increased risk was observed across all age groups and was greatest in infants and toddlers younger than 2 years. The increased risk was consistent across individual PPIs, and this increase was similar regardless of the time elapsed after PPI initiation (<90 days to more than 181 days), or cumulative duration of PPI treatment (30 days or less to more than a year) .

Strength and limitations: Strength of this study is the large population of children treated with PPIs, (80870) enabling not only ample statistical power both in primary analysis and sub analysis. Also, given the unselected nationwide population, results are likely generalizable to other similar populations

Limitations of the study include possibly underestimating asthma numbers as primary care settings were not included, lack of evidence that patients actually took the prescribed PPI's, and lack of data on OTC dispensed PPI's.

COMMENTARY

Proton pump inhibitors (PPIs) are among the most prescribed drugs worldwide and include Omeprazole, Esomeprazole, Lansoprazole, Pantoprazole, and Rabeprazole.

Nationwide healthcare registries from many countries – recently from Denmark and Ireland for example, have clearly documented multi-fold increase in PPI usage in infants and children. Similar trends have been found in other European countries, United States and also in our country.

PPI use in paediatrics is approved for children older than 1 year, for the short-term- treatment of symptomatic gastroesophageal reflux disease (GERD), healing of erosive esophagitis, treatment of peptic ulcer disease, and eradication of Helicobacter pylori. PPIs are the standard of care for paediatric eosinophilic esophagitis. Esomeprazole is the only PPI approved for use in patients 1 month to younger than 12 months of age.

Recommendations with available current evidence states that PPIs are not effective for treating symptoms such as unexplained crying, irritability, or sleep disturbance. usually attributed to GERD in otherwise healthy infants.

Notwithstanding the strict range of indications, PPIs are often empirically prescribed for reflux in infants , functional dyspepsia, chronic cough, and asthma without documented associated gastroesophageal reflux disease (GERD).

Acid secretion is stopped once the PPI attaches to the H^+-K^+-adenosine triphosphatase (H^+-K^+-ATPase) which is the enzyme responsible for acid secretion by the parietal cell in the stomach. Because of variations in binding to the enzyme, PPI's block acid secretion for various periods (e.g. Omeprazole for 24 h compared to 46 h for pantoprazole. Thus Proton pump inhibitors (PPI's) are known to alter both gut and lung microbiota through inhibition of gastric acid secretion. One known causative factor in the pathogenesis of asthma is the disturbance in the human microbiome.

The long-term gastric acid suppression in children has also been linked to increased risks of gastrointestinal and lower respiratory tract infections, bone fractures, and allergy. The evidence on the link between PPI usage and an increased risk of community-acquired pneumonia is mixed. In a prospective trial of PPI and ranitidine-

associated infections in new-borns, researchers discovered that both PPI and ranitidine usage over an 8-week period increased the risk of pneumonia (odds ratio 6.39, 95% CI 1.38–29.70) in the 4 months after enrolment. More recently, in New Zealand, a case-control study found no link between PPI usage and community-acquired pneumonia (n = 65) or lower respiratory tract infections (n = 566) in infants. The risk of respiratory tract infections in children related with PPI medications has yet to be determined.

A recent retrospective study from a national spontaneous reporting system database found seventy PPI-related adverse reaction reports in children (.01% of all database reports and 2% of all PPI adverse reaction reports, excluding literature cases), most of which were not serious or irreversible and presented with gastrointestinal (24%) and/or skin manifestations (21.3%). Notably, combination therapy (i.e., antibiotics) appeared to be positively linked with the severity of ADRs. In terms of short-term side effects, 34% of children using PPIs experience headaches, nausea, diarrhoea, or constipation . In children, chronic PPI usage has been associated to an increased risk of gastrointestinal and lower respiratory tract infections, bone fractures, and allergies. Although the toxicity profile of PPIs is unknown, particularly in children, pathogenetic pathways have been proposed, which are primarily connected to long-term gastric acid suppression.

Conclusion: The safety profiles of PPI usage, particularly chronic PPI use, have yet to be thoroughly defined. The risk of developing asthma however, is starkly clear from the present large cohort study. The authors observed a significant 57% increased risk of asthma among children who initiated PPI use compared with those who did not initiate PPI use. An increased risk was observed across all age groups and was greatest in infants and toddlers younger than 2 years. The finding was consistent across individual PPIs, and the risk increase was similar regardless of the cumulative duration of PPI treatment.

As clinicians, we must assess if a real indication exists before prescribing PPIs, considering the impact of PPI and the potential harmful effects on a child's future health. PPI's should be prescribed to children only when clearly indicated, weighing the potential benefit against potential harm

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