Lansoprazole Is Associated with Worsening Asthma Control in Children with the *CYP2C19* Poor Metabolizer Phenotype

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Abstract

Rationale: Gastric acid blockade in children with asymptomatic acid reflux has not improved asthma control in published studies. There is substantial population variability regarding metabolism of and response to proton pump inhibitors based on metabolizer phenotype. How metabolizer phenotype affects asthma responses to acid blockage is not known.

Objectives: To determine how metabolizer phenotype based on genetic analysis of *CYP2C19* affects asthma control among children treated with a proton pump inhibitor.

Methods: Asthma control as measured by the Asthma Control Questionnaire (ACQ) and other questionnaires from a 6-month clinical trial of lansoprazole in children with asthma was analyzed for associations with surrogates of lansoprazole exposure (based on treatment assignment and metabolizer phenotype). Groups included placebo-treated children; lansoprazole-treated extensive metabolizers (EMs); and lansoprazole-treated poor metabolizers (PMs). Metabolizer phenotypes were based on *CYP2C19* haplotypes.

Carriers of the *CYP2C19**2, *3, *8, *9, or *10 allele were PMs; carriers of two wild-type alleles were extensive metabolizers (EMs).

Measurements and Main Results: Asthma control through most of the treatment period was unaffected by lansoprazole exposure or metabolizer phenotype. At 6 months, PMs displayed significantly worsened asthma control compared with EMs (+0.16 vs. -0.13; $P = 0.02$) and placebo-treated children (+0.16 vs. -0.23; $P < 0.01$).

Differences in asthma control were not associated with changes in gastroesophageal reflux symptoms. Recent upper respiratory infection worsened asthma control, and this upper respiratory infection effect may be more pronounced among lansoprazole-treated PMs.

Conclusions: Children with the PM phenotype developed worse asthma control after 6 months of lansoprazole treatment for poorly controlled asthma. Increased exposure to proton pump inhibitor may worsen asthma control by altering responses to respiratory infections.

Clinical trial registered with www.clinicaltrials.gov (NCT00604851).

Keywords: child; polymorphism (genetics); phenotype; lansoprazole

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Asthma continues to cause extensive morbidity in children despite daily controller therapy (1). Gastroesophageal reflux (GER) commonly complicates the management of asthma, although the exact role GER plays in symptomatic asthma remains unknown. The possibility of occult gastroesophageal reflux contributing to refractory asthma led to SARCA (Study of Acid Reflux in Childhood Asthma), which studied lansoprazole, a gastric proton pump inhibitor (PPI), for the empiric treatment of uncontrolled asthma (2). Lansoprazole was ineffective at improving asthma control at the U.S. Food and Drug Administration–recommended dosing. Despite the reported futility of lansoprazole, use of PPIs has continued to be extremely common in the treatment of asthma (3). Previous studies in subjects with GER disease have shown that success of PPI treatment depends on genetics (4–6). In addition, many practitioners, aware of the substantial response variability (4, 5, 7, 8) and perceived relative safety of lansoprazole, may still elect to treat patients with asthma with a PPI with the rationale that particular “responder” patients may benefit.

The clinical effectiveness of PPI drugs is closely associated with plasma concentrations (9) and variation within the *CYP2C19* gene (10–12). Several loss-of-function *CYP2C19* single-nucleotide polymorphisms are fairly common in the population and consistently associate with higher PPI levels (13–16). From the SARCA cohort, we previously reported loss-of-function allele frequencies of 13, 20, and 30% for white, African American, and Asian children, respectively (10, 13). Assuming GER can elicit asthma symptoms, it would be rational to hypothesize that higher plasma levels of lansoprazole among poor hepatic metabolizers improve asthma control in this subgroup. Comparing asthma control among children with slow versus fast metabolism of lansoprazole would address the important question of whether slow metabolizers of PPI respond more favorably. If so, this would provide justification for testing a higher PPI dose for those with the extensive metabolizer phenotype—a group that makes up the majority of U.S. children.

Complicating the role of PPIs in asthma, one study reported that children who were poor metabolizers of lansoprazole

based on *CYP2C19* genotype had higher blood lansoprazole levels and were at significantly greater risk for upper respiratory infection (13). The mechanism for this association remains unclear, but could result from a protective effect of low gastric pH against colonization and infection with common respiratory pathogens, or from a direct action by lansoprazole (17, 18). Because rhinovirus and respiratory syncytial virus are leading causes of asthma exacerbations in children, it is also biologically plausible that higher PPI exposure (consistently seen among poor metabolizers [10, 13, 19]) could instead worsen asthma control. Therefore, we explored the effect of lansoprazole and metabolizer phenotype on asthma control by comparing longitudinal data among three groups (placebo-treated, lansoprazole-treated extensive metabolizers, and lansoprazole-treated poor metabolizers) in a 6-month asthma trial.

Methods

Details of the main study design have been published (2). All participants signed written informed consents. The parent SARCA study was approved by the Nemours Florida institutional review board (IRB) (82404-29) and by all other American Lung Association–Airways Clinical Research Center IRBs, and registered at ClinicalTrials.gov (NCT00604851). A total of 306 children 6 to 17 years old with poor asthma control while treated with inhaled corticosteroids were randomly assigned to either placebo ($n = 157$) or lansoprazole (15 mg/d for children weighing less than 30 kg or 30 mg/d for those weighing ≥ 30 kg) ($n = 149$) in a double-blinded manner for 6 months at 19 clinical sites from April 2007 to April 2011. The following was a post-hoc analysis involving 279 children (141 assigned to placebo and 138 assigned to lansoprazole) from the 306 SARCA participants who had specimens available for genotypic analysis.

Clinical Data

Changes in asthma control and GERD symptom assessment score were monitored over 6 months and compared among three groups previously shown to associate with increasing lansoprazole exposure (13) (placebo-treated children, lansoprazole-treated extensive metabolizers [EMs], and

lansoprazole-treated poor metabolizers [PMs]). Although in the current study we did not measure lansoprazole levels for the three groups, these groups were chosen as surrogates for likely increasing lansoprazole exposure on account of past work showing slower PPI metabolism in patients with one *CYP2C19* loss-of-function allele (10, 13, 19). The primary outcome measure was the change in the Asthma Control Questionnaire (ACQ) (2). The ACQ integrates seven components of asthma control, including five patient-reported asthma symptoms, need for bronchodilators, and pulmonary function; all are scored on a seven-point scale (0 to 6), with a higher score indicating worse asthma. A 0.4- to 0.5-point change in the ACQ score reflects a clinically important difference in asthma control (20, 21). Secondary outcomes included the Asthma Control Test (ACT), the childhood ACT, and the Asthma Symptom Utility Index (ASUI) (2). (See the online supplement for details of these measures.)

Digestive symptoms were measured with the Pediatric Gastroesophageal Reflux Disease Symptom Assessment Score (GSAS), which is a 10-item tool (22) that has been validated in children in the assessment of reflux disease and digestive symptoms such as chest/abdominal pain, pain/choking with eating, swallowing dysfunction, regurgitation, and nausea. It assesses symptom severity from the previous 7 days on an eight-point scale, with 0 and 7 indicating the least and greatest severity, respectively. A minimal important difference has not been established for the GSAS Questionnaire. Research staff conducted structured interviews at monthly clinic visits during the 6-month intervention period to assess symptom changes.

The occurrence of self-reported upper respiratory infections (URIs) was detected during the trial period from 6 visits at 1-month intervals, interviews of participants and caregivers about the presence or absence of various symptoms, or side effects that presented during the preceding month.

Laboratory Analyses

DNA isolation and *CYP2C19* genotyping has been previously described (13). Briefly, DNA was isolated from saliva (Oragene DNA kit; DNA Genotek Inc., Kanata, ON, Canada) or from blood collected at the randomization visit. Six *CYP2C19* single-nucleotide polymorphisms were genotyped:

NM_000769.1:c.680C>T/NM_000769.1:c.681G>A (rs6413438/rs4244285; *10/*2), NM_000769.1:c.636G>A (rs4986893; *3), NM_000769.1:c.358T>C (rs41291556; *8), NM_000769.1:c.431G>A (rs17884712; *9); and NM_000769.1:c.-806C>T (rs12248560; *17). Participants were classified as poor metabolizers (PMs) if they carried one or more *CYP2C19**10/*2, *3, *8, *9 alleles and extensive metabolizers (EMs) if they carried two wild-type alleles. DNA was genotyped by LightTyper fluorescence assay, using simple probe chemistry (Roche Applied Science, Indianapolis, IN) as

previously described (23). *CYP2C19* haplotypes were determined for each participant and associated with asthma control measures and GERD symptoms.

Data Analyses

Baseline data were collected before randomization and were summarized according to lansoprazole treatment and metabolizer phenotype. We used analysis of variance, chi-square, Wilcoxon, or Kruskal-Wallis tests as appropriate for comparing baseline characteristics among groups. Longitudinal models estimated the change

in questionnaire scores from baseline through 6 months, using generalized estimating equations with unstructured or exchangeable covariance matrices to adjust for repeated measures as previously described (2, 24). All models included male sex and race (black or other) as covariates. All participants with baseline and follow-up data and data on genotype status were included in the models to estimate the effect of lansoprazole treatment and metabolizer phenotype exposure. In the placebo group, we tested for an effect of metabolizer status (poor vs. extensive)

Table 1. Participant characteristics

	Treatment Group (n = 295)			P Value
	Placebo (n = 157)	EM (n = 94)	PM (n = 44)	
n	157	94	44	
Age (yr), mean (SD)	11 (3)	11 (3)	12 (3)	0.058
Male	102 (65%)	56 (60%)	24 (55%)	0.398
Race/ethnicity				0.317
Black	79 (50)	40 (43)	29 (66)	
White	52 (33)	36 (38)	11 (25)	
Hispanic	17 (11)	13 (14)	3 (7)	
Other	9 (6)	5 (5)	1 (2)	
Asthma characteristics				
Age at onset (yr), mean (SD)	3 (3)	3 (3)	4 (4)	0.425
Urgent asthma care in past year	109 (69)	69 (73)	36 (82)	0.259
Steroids in past year	98 (62)	69 (73)	33 (75)	0.107
Rescue inhaler 2 or more times/wk	118 (75)	71 (76)	31 (70)	0.977
Daily use of ICS/LABA	90 (57)	50 (53)	26 (60)	0.476
Daily use of leukotriene modifier	86 (55)	53 (56)	26 (59)	0.873
Baseline asthma scores, mean (SD)	156	94	44	
ACQ at screening*	1.6 (0.8)	1.6 (0.9)	1.5 (0.8)	0.626
ACQ at randomization*	1.2 (0.8)	1.2 (0.8)	1.1 (0.8)	0.702
ACT (12–17 yr) (n = 133) [†]	19 (14)	19 (4)	20 (4)	0.403
Children's ACT (5–11 yr) (n = 156) [‡]	20 (4)	20 (4)	20 (3)	0.801
Pulmonary function, mean (SD)	157	94	44	
FEV ₁ , percent predicted	92 (15)	91 (17)	92 (16)	0.757
FVC, percent predicted	101 (15)	100 (13)	102 (15)	0.821
Change in FEV ₁ postbronchodilator	8.5 (10.9)	10.5 (10.9)	11.1 (10.3)	0.059
Change in FVC postbronchodilator	2.0 (6.6)	3.4 (5.6)	2.5 (5.4)	0.041
Other chronic conditions				
GERD	2 (1)	2 (2)	1 (2)	0.701 (F)
Eczema	62 (39)	42 (45)	21 (48)	0.534
Rhinitis	80 (51)	65 (69)	28 (64)	0.014
Food allergies	43 (27)	22 (23)	11 (25)	0.777
Allergies worsen asthma	124 (79)	73 (78)	38 (86)	0.473
Exposed to secondhand smoke	52 (33)	26 (28)	9 (20)	0.238
Positive pH probes	20/53 (38)	18/36 (50)	8/20 (40)	0.504
GERD symptom score, [§] median (IQR)	9 (2, 22)	9 (1, 29)	6 (3, 16)	0.909
Number of symptoms, median (IQR)	2 (1, 4)	1 (0, 3)	1 (0, 2)	0.719

Definition of abbreviations: ACQ = Asthma Control Questionnaire; ACT = Asthma Control Test; EM = extensive metabolizer; F = Fisher exact test; GERD = gastroesophageal reflux disease; ICS = inhaled corticosteroid; IQR = interquartile range; LABA = long-acting β -agonist; PM = poor metabolizer.

Note: Values represent counts (%) unless otherwise indicated.

*Scores range from 0 to 6, with higher scores indicating worse asthma.

[†]Scores range from 5 to 25, with lower scores indicating worse asthma.

[‡]Scores range from 0 to 27, with lower scores indicating worse asthma.

[§]Scores range from 0 to 441, with higher values suggesting worse symptoms.

before collapsing data from those participants into one group regardless of metabolizer status. In an exploratory analysis, we investigated whether the effect of a URI on asthma control was modified by lansoprazole treatment and metabolizer phenotype by including time-dependent covariates for URI status at each visit with an interaction term for lansoprazole exposure. Analysis was performed with SAS version 9.2 (SAS Institute, Cary, NC) and STATA version 11 (StataCorp, College Station, TX).

Results

DNA was collected and analyzed from 279 of 306 participants. One hundred and forty-one participants were randomized to and received placebo and 138 were randomized to and received lansoprazole. Similar proportions of participants were classified as poor metabolizers in the placebo and lansoprazole group (31 vs. 32%, respectively; $P = 0.90$). Table 1 shows baseline data for these 279 participants according to the three lansoprazole treatment/metabolizer phenotype groups, that is, participants assigned to placebo regardless of metabolizer status, and participants assigned to lansoprazole and who were classified as extensive or poor metabolizers. At baseline, there was an association between lansoprazole/metabolizer phenotype group and FVC change after bronchodilator and the prevalence of rhinitis. There was no significant association between race and metabolizer status. Otherwise, baseline demographic, asthma, and comorbidity characteristics were similar between groups. The call rate for the genotypes was greater than 98%. The allele frequencies for *CYP2C19**10/*2, *3, *8, *9, and *17 by race/ethnic group were previously published and are in accord with previous work (13, 25).

To address our hypothesis that changes in asthma control with lansoprazole treatment could be related to *CYP2C19* genotype, we compared longitudinal asthma control scores during the 6-month intervention period according to lansoprazole treatment/metabolizer phenotype group (Figure 1 and Table 2). Asthma control scores were similar between placebo-treated and lansoprazole-treated extensive metabolizers throughout the 6-month treatment period. At 6 months, the PM group did not have

Figure 1. Change in Asthma Control Questionnaire (ACQ) score in children with uncontrolled asthma by level of lansoprazole exposure. Higher scores indicate worse asthma control. Error bars indicate 95% confidence intervals. There is zero suppression on the y axis. EM = lansoprazole-treated extensive metabolizer; Plb = placebo; PM = lansoprazole-treated poor metabolizer.

improved asthma control, as was hypothesized. Instead, we found that the PM group had a statistically significant increase in ACQ score, signifying worse asthma control. At study completion, PMs experienced significantly worsened asthma control compared with EMs (+0.16 vs. -0.13; $P = 0.02$) and placebo-treated children (+0.16 vs. -0.23; $P < 0.01$) (Table 2; and see Figure E1 in the online supplement).

We found a similar pattern trending toward asthma worsening at 6 months among lansoprazole-treated PM participants when using the childhood ACT but not when assessing symptoms using the ASUI (Table 2). There was no association between lansoprazole treatment/metabolizer phenotype group and change in GERD assessment score or in the number of daily GER-related symptoms (Table 3). As was seen in the full trial population, there were no asthma treatment effects (lansoprazole vs. placebo) in this subgroup of participants (Tables 2 and 3).

During the intervention period, participants who experienced a URI reported significantly worse asthma control assessed at the next monthly clinic visit, regardless of intervention (Figures E2 and E3). On average the ACQ score was 0.3 points higher (worse asthma; $P < 0.0001$) in participants with a URI in the preceding period. The difference in asthma control between URI-affected and URI-nonaffected children among the PMs taking

lansoprazole (compared with EMs treated with lansoprazole and placebo treated) showed a nonsignificant trend and consistently exceeded the 0.4–0.5 minimal important difference for the ACQ test (Figure 2), whereas the similar URI effects in placebo-treated and lansoprazole-treated EMs did not reach the level of clinic importance. At the 6-month visit, when asthma control was significantly worse among lansoprazole-treated PMs, the mean differences (95% confidence interval) in ACQ between those affected and not affected by recent URI were 0.383 (0.108, 0.657), 0.277 (-0.092, 0.646), and 0.852 (0.358, 1.347) for placebo-treated children, lansoprazole-treated EMs, and lansoprazole-treated PMs, respectively ($P = 0.17$, two-way; Figure 2).

Discussion

Our results suggest that in this cohort, members of which on average did not display PPI-related improvements, there was no evidence of improved asthma response based on metabolizer phenotype. Instead, the subgroup given lansoprazole and who were poor metabolizers developed worse asthma control at 6 months. Therefore, clinicians caring for children with refractory asthma treated with inhaled corticosteroids and without substantial acid reflux would be unwise to initiate proton pump inhibitor therapy because patients

Table 2. *CYP2C19* genotype, lansoprazole treatment, and asthma control*

	Placebo		Lansoprazole				<i>P</i> Values for Pairwise Comparisons [†]		
	n	All	n	EM	n	PM	Plb vs. EM	Plb vs. PM	EM vs. PM
ACQ[‡]									
Baseline	141	1.16	94	1.11	44	1.05	0.57	0.38	0.67
3 mo	121	1.08	81	1.00	41	0.92			
Δ3 mo		-0.09		-0.12		-0.13	0.81	0.79	0.94
6 mo	120	0.93	83	0.98	40	1.21			
Δ6 mo		-0.23		-0.13		+0.16	0.97	<0.01	0.02
c-ACT[§]									
Baseline	78	19.7	53	19.5	18	19.9	0.73	0.87	0.67
3 mo	64	21.2	44	20.6	16	20.8	0.66	0.76	0.47
Δ3 mo		1.4		1.1		0.8			
6 mo	60	21.6	41	21.5	16	19.9	0.88	0.08	0.07
Δ6 mo		1.9		2.0		0.0			
ACT									
Baseline	60	18.5	39	19.0	25	19.8	0.54	0.13	0.40
3 mo	51	20.1	33	19.7	23	20.6	0.31	0.29	0.92
Δ3 mo		1.6		0.7		0.8			
6 mo	55	20.1	38	20.5	22	20.0	0.89	0.09	0.10
Δ6 mo		1.6		1.5		0.2			
ASUI									
Baseline	141	0.82	94	0.83	44	0.83	0.54	0.83	0.84
3 mo	122	0.85	81	0.85	41	0.86	0.54	0.82	0.53
Δ3 mo		0.03		0.02		0.04			
6 mo	122	0.88	84	0.87	40	0.84	0.26	0.17	0.51
Δ6 mo		0.06		0.04		0.01			

Definition of abbreviations: ACQ = Asthma Control Questionnaire; ACT = Asthma Control Test (age, ≥12); ASUI = Asthma Symptom Utility Index; c-ACT = childhood Asthma Control Test (age, 5–11); EM = extensive metabolizer; Plb = placebo; PM = poor metabolizer.

**P* values for treatment effects (lansoprazole vs. placebo) from general estimating equation models including treatment status, all measurement time points, interactions with treatment status at each time point, sex, and black race. Estimates not included in table.

[†]*P* values and model estimates for pairwise comparisons of placebo (all), extensive metabolizers assigned to lansoprazole, and poor metabolizers assigned to lansoprazole from general estimating equation models including lansoprazole exposure status (placebo or EM or PM), all time points, and interactions with lansoprazole exposure at each time point, sex, and black race.

[‡]Scores range from 0 to 6 with higher scores indicating worse asthma.

[§]Scores range from 0 to 27 with lower scores indicating worse asthma.

^{||}Scores range from 5 to 25 with lower scores indicating worse asthma.

^{||}Scores range from 0 to 1, with higher values suggesting reduced symptoms.

may be made worse. It is important to note that the risk–benefit relationship of PPI use among patients with asthma with problematic acid reflux is likely to be different than that seen in the current cohort and requires further study.

These results are important to providers treating children because for the first time we report that children with asthma treated with PPI develop worse asthma control in relation to their metabolizer phenotype. These results require replication and mechanistic study. In the current study, poor metabolizers taking lansoprazole developed significantly worse asthma control compared with both lansoprazole-treated extensive metabolizers and placebo-treated children. The 0.39 difference in ACQ score approached but did not exceed the minimal clinically important

difference of 0.4–0.5 (20, 21). Worsening of asthma control within the poor metabolizer group occurred after 5 months of lansoprazole treatment, and it is not known whether extended therapy would result in even further worsening. This may be an important question to answer because PPIs are commonly used over extended durations and the poor metabolizer phenotype is fairly common. Strom and colleagues (26) have estimated that the prevalence of one or more loss-of-function alleles in *CYP2C19* ranges from 22 to 30% depending on ethnicity. The change in ACQ score seen among poor metabolizers is likely to reflect a true effect (and not a type I error) because similar worsening in asthma control was corroborated by both similar, although nonsignificant differences in childhood and adult ACT scores.

A limitation of the current study is its post-hoc nature. Post-hoc analyses are important for the generation of scientific hypotheses but should be regarded with skepticism until results are replicated. An additional limitation is that we did not perform area under the plasma concentration–time curve (AUC) or pharmacodynamic gastric pH testing on the current cohort. However, past researchers have shown that patients with one loss-of-function allele for *CYP2C19* consistently display higher peak proton pump inhibitor drug levels (13), higher AUCs (10, 11, 15, 16, 19), and reduced gastric pH (16, 19), which supports the likelihood that future patients with one loss-of-function allele given a PPI will experience greater drug exposure compared with patients with two normal alleles.

The current study was not able to determine a mechanism of action. However, we previously reported from the same cohort that the PM phenotype was associated with higher lansoprazole plasma levels and greater risk for subsequent URI and sore throat (13). In the current study, we found that among children with a recent URI during the study, PMs treated with lansoprazole had the greatest mean worsening of asthma control compared with EMs and the placebo-treated participants. Although the effect does not reach the level of statistical significance, the URI-related differences in ACQ exceed the clinically meaningful difference threshold only in the PM-lansoprazole group. Our analysis was not powered to detect this effect and is a major limitation. We can only say that these results are consistent with greater lansoprazole exposure in PMs increasing the risk for virally induced loss of asthma control. Further study with larger cohorts is needed. Viral URIs are well-known triggers for asthma symptoms. Acid suppression has been associated with prolonged retention of influenza in gastric epithelium, suggesting that low gastric pH contributes to antiviral defenses (27) and viral clearance. It is possible that acidic refluxate may play a protective role reducing either viral infections or virus-associated pathogenic bacteria, which have been found to contribute to the severity of asthma exacerbations (28).

Previous studies have reported increased respiratory infections (13) and community-acquired pneumonia (29, 30) in patients treated with PPIs. The link

Table 3. *CYP2C19* genotype, lansoprazole treatment, and gastroesophageal reflux symptoms*

	Placebo		Lansoprazole				<i>P</i> Values for Pairwise Comparisons [†]		
	n	All	n	EM	n	PM	Plb vs. EM	Plb vs. PM	EM vs. PM
GSAS score [‡]									
Baseline	141	20	94	20	43	18	0.64	0.95	0.68
Δ3 mo		−6		−7		3	0.76	0.95	0.68
Δ6 mo		−8		−6		−4	0.71	0.38	0.60
Number of daily symptoms									
Baseline	141	3	94	3	43	3	0.64	0.43	0.90
Δ3 mo		−1		−1		−1	0.97	0.89	0.90
Δ6 mo		−1		−1		−1	0.09	0.52	0.60

Definition of abbreviations: EM = extensive metabolizer; GSAS = GERD (gastroesophageal reflux disease) Symptom Assessment Score; Plb = placebo; PM = poor metabolizer.

**P* values for treatment effects (lansoprazole vs. placebo) from general estimating equation models including treatment status, all measurement time points, interactions with treatment status at each time point, sex, and black race. Estimates not included in table.

[†]*P* values and model estimates for pairwise comparisons of placebo (all), extensive metabolizers assigned to lansoprazole, and poor metabolizers assigned to lansoprazole from general estimating equation models including lansoprazole exposure status (placebo or EM or PM), all time points, and interactions with lansoprazole exposure at each time point, sex, and black race.

[‡]Scores range from 0 to 441, with higher values suggesting worse symptoms.

between PPI use and community-acquired pneumonia has been questioned because of possible confounding by indication and protopathic bias (31). In a study that avoids these potential biases, we showed that the odds of upper respiratory infection in

asthmatic children were proportional to *CYP2C19* haplotype and metabolizer phenotype (13). Several lines of evidence suggest that PPIs and subsequent respiratory infections have biological plausibility. The low pH of gastric acid

forms a bactericidal defense by reducing survival of many gut and respiratory pathogens and by regulating competing gastric microflora. Gastrointestinal dysfunction, a common sequelae of PPI use, increases the risk for bacterial colonization of the lungs (32, 33). PPIs can impair cell-mediated immune defenses (17, 18), and can impair leukocyte function particularly after extended PPI courses (34, 35). This may be pertinent because worsening asthma control in our 6-month trial did not occur until after 4 months. Therefore, we speculate that poor metabolizers of lansoprazole on account of having one or more loss-of-function *CYP2C19**10/*2, *3, *8, *9 alleles have slower clearance of lansoprazole, enhanced acid suppression, and delayed clearance of virus and virus-associated asthmagenic bacteria. Because respiratory viruses constitute the most common trigger for loss of asthma control in children, suppression of gastric acid may pose a long-term threat to asthma control. Over extended treatment periods, children with slow PPI metabolism are likely to be at increased risk for virally induced loss of asthma control.

Our findings, although exploratory, are important and stress the need for further study in the relationship between acid suppression treatments and respiratory diseases in children, in whom acid suppression treatment is common. The prevalence of PPI use is extremely high in children with bronchopulmonary dysplasia and cystic fibrosis (CF), as well as in children with asthma with symptomatic GER. Most accredited CF centers report that the prevalence of acid suppression therapy for pancreatic-insufficient children is greater than 60% (36). Any exposure that increases respiratory viral risk is likely to worsen the long-term lung health of vulnerable populations such as patients with CF (37, 38). In addition, GER is reported in up to 80% of patients with asthma. Short-acting β -agonists, the most commonly used antiasthma medication, can reduce lower esophageal sphincter tone and may contribute to GER among patients with asthma. A deleterious effect of PPIs on asthma control contradicts the commonly held view among many pediatric providers that PPIs are uniformly safe. Related to this widespread view, the use of PPIs in children has now reached the level of 5% of all U.S. children (39).

In addition, many children continue to take PPI medications much longer than the 24-week treatment period of this study. In

Figure 2. Difference in Asthma Control Questionnaire (ACQ) scores between patients with recent upper respiratory infection (URI) and those without (calculated as $ACQ_{URI} - ACQ_{no\ URI}$). Shown is the difference by metabolizer phenotypes over the 6-month treatment period. EM = lansoprazole-treated extensive metabolizer; Plb = placebo; PM = lansoprazole-treated poor metabolizer.

fact, the Centers for Medicare and Medicaid Services (CMS) have published the concern that providers commonly use PPIs beyond their approved dosage, duration, and indication (40). Last, because roughly 30% of the population carry at least one loss-of-function allele and have delayed PPI clearance (13, 25), the relationship between PPIs and asthma control is a substantial public health and economic issue. Our study supports the need for pharmacokinetic studies specifically among patients with GER and PPI poor metabolizers to determine optimal dosing for children with asthma. This study was conducted in patients without underlying reflux, so it is an open question whether *CYP2C19* metabolizer status in patients with asthma with symptomatic reflux will affect asthma responses to PPI.

With the possibility that high PPI exposure could contribute to poor asthma control and the still uncertain role of GER in asthma morbidity, more investigation is needed, focusing on the best role for PPIs in the setting of asthma and symptomatic GER. Considering the high prevalence of GER and PPI use among patients with asthma and the prevalence of PM status, it is possible that PPI use may be contributing to the problem of uncontrolled asthma. It further supports caution in PPI prescribing among pediatric prescribers and suggests the need for additional long-term safety studies in children. ■

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References

- 1 Sorkness CA, Lemanske RF Jr, Mauger DT, Boehmer SJ, Chinchilli VM, Martinez FD, Strunk RC, Szeffler SJ, Zeiger RS, Bacharier LB, *et al.*; Childhood Asthma Research and Education Network of the National Heart, Lung, and Blood Institute. Long-term comparison of 3 controller regimens for mild–moderate persistent childhood asthma: the Pediatric Asthma Controller Trial. *J Allergy Clin Immunol* 2007; 119:64–72.
- 2 Holbrook JT, Wise RA, Gold BD, Blake K, Brown ED, Castro M, Dozor AJ, Lima JJ, Mastronarde JG, Sockrider MM, *et al.*; Writing Committee for the American Lung Association Asthma Clinical Research Centers. Lansoprazole for children with poorly controlled asthma: a randomized controlled trial. *JAMA* 2012;307:373–381.

- 3 Blake K, Teague WG. Gastroesophageal reflux disease and childhood asthma. *Curr Opin Pulm Med* 2013;19:24–29.
- 4 Furuta T, Ohashi K, Kosuge K, Zhao XJ, Takashima M, Kimura M, Nishimoto M, Hanai H, Kaneko E, Ishizaki T. CYP2C19 genotype status and effect of omeprazole on intragastric pH in humans. *Clin Pharmacol Ther* 1999;65:552–561.
- 5 Shirai N, Furuta T, Xiao F, Kajimura M, Hanai H, Ohashi K, Ishizaki T. Comparison of lansoprazole and famotidine for gastric acid inhibition during the daytime and night-time in different CYP2C19 genotype groups. *Aliment Pharmacol Ther* 2002;16:837–846.
- 6 Sugimoto M, Furuta T, Shirai N, Nakamura A, Kajimura M, Hishida A, Ohashi K, Ishizaki T. Comparison of an increased dosage regimen of rabeprazole versus a concomitant dosage regimen of famotidine with rabeprazole for nocturnal gastric acid inhibition in relation to cytochrome P450 2C19 genotypes. *Clin Pharmacol Ther* 2005;77:302–311.
- 7 Furuta T, Shirai N, Xiao F, Ohashi K, Ishizaki T. Effect of high-dose lansoprazole on intragastric pH in subjects who are homozygous extensive metabolizers of cytochrome P4502C19. *Clin Pharmacol Ther* 2001;70:484–492.
- 8 Kawamura M, Ohara S, Koike T, Iijima K, Suzuki J, Kayaba S, Noguchi K, Hamada S, Noguchi M, Shimosegawa T; Study Group of GERD. The effects of lansoprazole on erosive reflux oesophagitis are influenced by CYP2C19 polymorphism. *Aliment Pharmacol Ther* 2003;17:965–973.
- 9 Litalien C, Théorêt Y, Faure C. Pharmacokinetics of proton pump inhibitors in children. *Clin Pharmacokinet* 2005;44:441–466.
- 10 Furuta T, Shirai N, Sugimoto M, Ohashi K, Ishizaki T. Pharmacogenomics of proton pump inhibitors. *Pharmacogenomics* 2004;5:181–202.
- 11 Furuta T, Shirai N, Sugimoto M, Nakamura A, Hishida A, Ishizaki T. Influence of CYP2C19 pharmacogenetic polymorphism on proton pump inhibitor-based therapies. *Drug Metab Pharmacokinet* 2005;20:153–167.
- 12 Hagymási K, Müllner K, Herszényi L, Tulassay Z. Update on the pharmacogenomics of proton pump inhibitors. *Pharmacogenomics* 2011;12:873–888.
- 13 Lima JJ, Lang JE, Mougey EB, Blake KB, Gong Y, Holbrook JT, Wise RA, Teague WG. Association of CYP2C19 polymorphisms and lansoprazole-associated respiratory adverse effects in children. *J Pediatr* 2013;163:686–691.
- 14 Lima JJ, Franciosi JP. Pharmacogenomic testing: the case for CYP2C19 proton pump inhibitor gene–drug pairs. *Pharmacogenomics* 2014;15:1405–1416.
- 15 Gawrońska-Szklarz B, Adamiak-Giera U, Wyska E, Kurzawski M, Gornik W, Kaldonska M, Drozdziak M. CYP2C19 polymorphism affects single-dose pharmacokinetics of oral pantoprazole in healthy volunteers. *Eur J Clin Pharmacol* 2012;68:1267–1274.
- 16 Hayato S, Hasegawa S, Hojo S, Okawa H, Abe H, Sugisaki N, Munesue M, Horai Y, Ohnishi A. Dose–response relationships of rabeprazole 5, 10, 20, and 40 mg once daily on suppression of gastric acid secretion through the night in healthy Japanese individuals with different CYP2C19 genotypes. *Eur J Clin Pharmacol* 2012;68:579–588.
- 17 Aybay C, Imir T, Okur H. The effect of omeprazole on human natural killer cell activity. *Gen Pharmacol* 1995;26:1413–1418.
- 18 Capodicasa E, De Bellis F, Pelli MA. Effect of lansoprazole on human leukocyte function. *Immunopharmacol Immunotoxicol* 1999;21:357–377.
- 19 Sugimoto M, Furuta T, Shirai N, Kajimura M, Hishida A, Sakurai M, Ohashi K, Ishizaki T. Different dosage regimens of rabeprazole for nocturnal gastric acid inhibition in relation to cytochrome P450 2C19 genotype status. *Clin Pharmacol Ther* 2004;76:290–301.
- 20 Juniper EF, Gruffydd-Jones K, Ward S, Svensson K. Asthma Control Questionnaire in children: validation, measurement properties, interpretation. *Eur Respir J* 2010;36:1410–1416.
- 21 Nguyen JM, Holbrook JT, Wei CY, Gerald LB, Teague WG, Wise RA. Validation and psychometric properties of the Asthma Control Questionnaire among children. *J Allergy Clin Immunol* 2014;133:91–7 .e1–6.
- 22 Deal L, Gold BD, Gremse DA, Winter HS, Peters SB, Fraga PD, Mack ME, Gaylord SM, Tolia V, Fitzgerald JF. Age-specific questionnaires distinguish GERD symptom frequency and severity in infants and young children: development and initial validation. *J Pediatr Gastroenterol Nutr* 2005;41:178–185.
- 23 Lima JJ, Mohapatra S, Feng H, Lockey R, Jena PK, Castro M, Irvin C, Johnson JA, Wang J, Sylvester JE. A polymorphism in the NPPA gene associates with asthma. *Clin Exp Allergy* 2008;38:1117–1123.
- 24 Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics* 1986;42:121–130.
- 25 Saito Y, Maekawa K, Ozawa S, Sawada J. Genetic polymorphisms and haplotypes of major drug metabolizing enzymes in East Asians and their comparison with other ethnic populations. *Curr Pharmacogenomics Person Med* 2007;5:49–78.
- 26 Strom CM, Goos D, Crossley B, Zhang K, Buller-Burke A, Jarvis M, Quan F, Peng M, Sun W. Testing for variants in CYP2C19: population frequencies and testing experience in a clinical laboratory. *Genet Med* 2012;14:95–100.
- 27 Hayase Y, Tobita K, Sato H. Detection of type B influenza virus genes from biopsied gastric mucosa. *J Gastroenterol* 2002;37:101–105.
- 28 Kloepper KM, Lee WM, Pappas TE, Kang TJ, Vrtis RF, Evans MD, Gangnon RE, Bochkov YA, Jackson DJ, Lemanske RF Jr, et al. Detection of pathogenic bacteria during rhinovirus infection is associated with increased respiratory symptoms and asthma exacerbations. *J Allergy Clin Immunol* 2014;133:1301–1307, 1307.e1–3.
- 29 Laheij RJ, Sturkenboom MC, Hassing RJ, Dieleman J, Stricker BH, Jansen JB. Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs. *JAMA* 2004;292:1955–1960.
- 30 Canani RB, Cirillo P, Roggero P, Romano C, Malamisura B, Terrin G, Passariello A, Manguso F, Morelli L, Guarino A; Working Group on Intestinal Infections of the Italian Society of Pediatric Gastroenterology, Hepatology and Nutrition (SIGENP). Therapy with gastric acidity inhibitors increases the risk of acute gastroenteritis and community-acquired pneumonia in children. *Pediatrics* 2006;117:e817–e820.
- 31 Jena AB, Sun E, Goldman DP. Confounding in the association of proton pump inhibitor use with risk of community-acquired pneumonia. *J Gen Intern Med* 2013;28:223–230.
- 32 Inglis TJ, Sherratt MJ, Sproat LJ, Gibson JS, Hawkey PM. Gastrointestinal dysfunction and bacterial colonisation of the ventilated lung. *Lancet* 1993;341:911–913.
- 33 Ruhl CE, Sonnenberg A, Everhart JE. Hospitalization with respiratory disease following hiatal hernia and reflux esophagitis in a prospective, population-based study. *Ann Epidemiol* 2001;11:477–483.
- 34 Abraham NS. Proton pump inhibitors: potential adverse effects. *Curr Opin Gastroenterol* 2012;28:615–620.
- 35 Zedtwitz-Liebenstein K, Wenisch C, Patruta S, Parschalk B, Daxböck F, Graninger W. Omeprazole treatment diminishes intra- and extracellular neutrophil reactive oxygen production and bactericidal activity. *Crit Care Med* 2002;30:1118–1122.
- 36 Cystic Fibrosis Foundation. Patient registry annual data report 2012. Bethesda, MD: Cystic Fibrosis Foundation; 2012.
- 37 Frickmann H, Jungblut S, Hirche TO, Gross U, Kuhns M, Zautner AE. Spectrum of viral infections in patients with cystic fibrosis. *Eur J Microbiol Immunol* 2012;2:161–175.
- 38 Cohen TS, Prince A. Cystic fibrosis: a mucosal immunodeficiency syndrome. *Nat Med* 2012;18:509–519.
- 39 Taylor A. Pediatric focused safety review: proton pump inhibitors: esomeprazole, lansoprazole, omeprazole, rabeprazole. Washington, DC: U.S. Food and Drug Administration; 2010.
- 40 CMS Medicaid Integrity Program (MIP). Proton pump inhibitors: use in pediatric patients [fact sheet]. Washington, DC: MIP, Center for Medicare and Medicaid Services, Department of Health and Human Services; 2013.