Normal and Proton Pump Inhibitor–Mediated Gastrin Levels in Infants 1 to 11 Months Old

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ABSTRACT

Background: Scant data exist on the normal range of serum gastrin in infants. In phase I and III trials of rabeprazole in gastroesophageal reflux disease, we studied serum gastrin levels in infants 1 to 11 months old, and assessed normal ranges and the effect of acid-suppressive drugs.

Methods: Overall, 349 treatment-naïve or treatment-experienced (previously exposed to proton pump inhibitors and/or H_2-receptor antagonists) infants with gastroesophageal reflux disease were screened for baseline serum gastrin. Repeat gastrin was monitored at early termination or end of study, allowing assessment of 1 to 8 week daily rabeprazole (5- or 10-mg) treatment on gastrin levels.

Results: Median (5%–95% range) baseline gastrin was 118 ng/L (39–315) in the treatment-naïve group (n = 251), driven mostly by high levels (121.5 [48–326] ng/L) in the 1- to <4-month-old subgroup. Treatment-experienced infants (n = 98) had elevated baseline gastrin levels (152 [48–487] ng/L; $P = 0.0011$) with no clear difference between previously proton pump inhibitor–exposed and H_2-receptor antagonist–exposed groups. At the end of study, mean (standard deviation) levels were unchanged from baseline in infants withdrawn from rabeprazole to placebo (124 [94] ng/L), but elevated from baseline in those continuing treatment with 5-mg (245 [151] ng/L) and 10-mg (332 [222] ng/L) rabeprazole during the study.

Conclusions: Gastrin levels in treatment-naïve infants were elevated through 8 months of age. Between 8 and 12 months of age, they declined so that the median level was within the upper limit of the normal adult range (<100 ng/L). Previous exposure to acid-suppressive medications and short-term exposure to rabeprazole significantly increased gastrin levels in infants younger than 1 year.

Key Words: gastrin, gastroesophageal reflux disease, infants, proton pump inhibitor

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Gastrin is secreted from antral G cells in response to peptides and amino acids in food, gastric distention, vagal stimulation, and hypercalcemia. It generates hydrogen ion production in the stomach principally by stimulating histamine release in enterochromaffin (ECL) cells, and also by a direct action on parietal cell proton pumps. Serum gastrin levels are lowest during fasting and are increased during feeding. Other conditions that result in increased gastrin are H_2-receptor antagonist (H_2RA)– and proton pump inhibitor (PPI)–induced gastric acid suppression; loss of parietal cell mass with ensuing hypochlorhydria caused by *Helicobacter pylori* infection and other inflammatory conditions; and gastrin secreting tumors (Zollinger-Ellison syndrome) (1). Normal ranges for fasting serum gastrin in adults are well described, fostering the recognition of conditions associated with hypergastrinemia; however, corresponding data defining normal fasting serum gastrin levels in infants are scanty. In a textbook of pediatrics, the normal range for newborns is listed as 20 to 300 ng/L and for ''children'' as 10 to 125 ng/L (1). Most reference laboratories quote the normal fasting gastrin values in adults as <100 ng/L and have no corresponding values for children or infants. Several earlier studies have documented increased serum gastrin levels in newborns and infants in the first 4 months of life (2,3). The natural history of elevated neonatal serum gastrin levels has not been systematically studied in a large group of infants during the first year of life, however.

The use of acid-suppressive drugs, chiefly H_2RAs and PPIs, results in suppression of gastric acid secretion with reflexive increased gastrin secretion and hypergastrinemia. In adults, serum gastrin levels are increased because of the prolonged use of PPIs (4). Pathologists have described parietal cell hypertrophy and fundic gland polyps in gastric biopsy specimens of patients receiving long-term PPI treatment, which is thought to be the result of hypergastrinemia and ECL cell hyperplasia (5). Some studies have also documented increased serum gastrin levels in children younger than 1 year with gastroesophageal reflux–induced esophagitis following treatment with PPIs (6). A recent article in this age group documents ECL cell hyperplasia in approximately 11% of children treated with omeprazole for 3 to 21 months (7); however, there are scant data on the effect of exposure to H_2RAs and PPIs on serum gastrin levels in infants younger than 1 year.

During both a phase I and a phase III study of rabeprazole treatment of symptomatic gastroesophageal reflux disease (GERD) in infants ages 1 to 11 months, baseline fasting serum gastrin levels were obtained from infants who were otherwise healthy except for

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having symptoms of GERD. Infants included both those previously exposed to H_2RAs and/or PPIs as well as those with no previous exposure. In addition, in the phase III study, end of study (EOS) fasting serum gastrin levels were obtained following 1 to 8 weeks of rabeprazole exposure. This allowed us to compile and analyze a large dataset of fasting serum gastrin levels in infants 1 to 11 months old.

The primary objective of this post hoc analysis was to determine the range of fasting serum gastrin levels in 1- to 11-month-old infants with symptomatic GERD who were both treatment naïve and previously exposed to acid-suppressive medications. The secondary objective was to document the effect of short-term exposure of the PPI rabeprazole on serum gastrin levels. The results suggest a physiologic hypergastrinemia that decreases but persists above adult levels through the first year of life, and a significant increase in fasting serum gastrin in response to drug-induced acid suppression, most prominently displayed in the youngest infants.

METHODS

Infants 1 to 11 months old (corrected age >44 weeks) of either sex weighing between 3.4 and 14 kg (inclusive), who had an investigator-determined diagnosis of symptomatic GERD, were enrolled. The diagnosis of symptomatic GERD was based on the presence of recurrent vomiting and additional symptoms of irritability, crying, feeding dysfunction, arching, and other symptoms on a GERD symptom score (I-GERQ-R) with a total score of >16 (8). Infants were drawn from 2 studies (a phase I and a phase III study), both of which mandated the same age range, weight range, and symptomatic diagnosis for inclusion. A medical history, including the type and duration of previous exposure to acid-suppressive drugs, was obtained. In infants previously treated with acid-suppressive drugs before enrollment, all H_2RAs and/or PPIs were discontinued at least 72 hours before blood sample collection. Baseline serum gastrin levels were analyzed as part of a menu of safety laboratory parameters after observation of potential infants during a screening period confirmed the diagnosis of symptomatic GERD. Gastrin levels were obtained a minimum of 3 hours post-feeding in the youngest infants and after 4 to 8 hours of fasting in the older infants.

The study protocols of both the studies (phase I and phase III) were approved by the independent ethics committee or institutional review board, and the studies were conducted in accordance with the ethical principles originating in the Declaration of Helsinki and in accordance with the International Conference on Harmonization Good Clinical Practice guidelines, applicable regulatory requirements, and in compliance with the protocol. Parents or legally accepted representatives of children provided written informed consent before participation in the study.

Infants in the phase I study were treated with rabeprazole, either 5 or 10 mg (randomized 1:1) once daily at the same time each morning for 5 days, and underwent measurements of rabeprazole plasma concentrations and prolonged intraesophageal and intragastric pH at baseline and on days 1 and 5 of treatment. Only baseline, and not EOS, serum gastrin values from this study were analyzed because of the limited short-term rabeprazole exposure in these infants. Infants in the phase III study were treated with rabeprazole for a minimum of 1 week and a maximum of 8 weeks. All of the infants who met inclusion criteria of symptomatic GERD and had I-GERQ-R score >16 were enrolled in an open-label (OL) period during which they received 10-mg rabeprazole once daily for 1 to 3 weeks (median 20 days) (8). Infants who improved clinically, as rated by their primary caregiver (good or excellent on a Clinical Global Impression of Improvement scale) during the OL period, were randomized (1:1:1) into a double-blind placebo-controlled withdrawal period (DB) during which they continued to receive rabeprazole 10 mg daily (median 35 days) or decreased to 5 mg daily (median 31 days), or were withdrawn to a daily placebo (median 33 days).

The baseline fasting gastrin levels in infants from this study were combined with those from the phase I study for analysis. An EOS fasting serum gastrin level was obtained as part of the EOS safety laboratory parameters at the end of 5 weeks of the DB period or at early termination from the phase III study. The EOS serum gastrin was compared with the baseline values to ascertain the effect of PPI exposure on gastrin levels.

Serum gastrin concentration was measured by a standard radioimmunoassay technique that measures both G34 and G17 components of gastrin with equimolar potency (9). Blood samples were drawn by venipuncture after at least 3 hours of fasting even in the youngest infants. To provide an estimated normal range of serum gastrin values in infants that could be compared with the normal adult range, without making additional assumptions about the distribution of observed data, a descriptive summary (median and range) was provided for baseline serum gastrin levels in the total group and age subgroups. In addition, statistical comparisons were provided for baseline serum gastrin levels in total treatment-experienced versus treatment-naïve infants, and treatment-experienced versus treatment-naïve infants in age subgroups (1–<4 months of age, 4–<8 months, and 8–<12 months). In infants in the phase III study, the EOS serum gastrin levels following rabeprazole treatment were compared with baseline levels, and were compared between groups of infants exposed to 10-mg rabeprazole versus 5-mg rabeprazole versus those withdrawn to placebo.

RESULTS

For purposes of the analysis of baseline serum gastrin levels, infants were categorized into treatment-naïve infants who were treated with conservative measures for GERD but not treated with H_2RAs or PPIs before enrollment (n = 251) and treatment-experienced infants who were exposed to either H_2RAs or PPIs or both before enrollment (n = 98). The duration of exposure was similar in H_2RA-experienced infants (mean [standard deviation, SD] 60.6 [62.3] days; median 30.5 days; range 4–281 days) and in PPI-experienced infants (mean [SD] 54.9 [56.5] days; median 36.0 days; range 2–197 days). The mean dose per kilogram per day of both H_2RAs and PPIs given previously is summarized in Table 1 and falls within the usual recommended ranges in the majority of infants.

Figure 1 shows a box-and-whisker plot of the baseline serum gastrin levels in the treatment-naïve and treatment-experienced infants. The treatment-naïve infants had significantly lower median baseline serum gastrin levels (118.0 ng/L; 5%–95% range 39–315 ng/L) compared with treatment-experienced infants (152.0 ng/L; 5%–95% range 48–487 ng/L; $P = 0.0011$). Figure 2 shows the baseline serum gastrin in the treatment-naïve versus treatment-experienced group divided by age subgroups (1–<4 months, n = 136; 4–<8 months, n = 84; 8–<12 months, n = 31). In the treatment-naïve group, the median (5%–95% range) serum gastrin levels decreased from 121.5 ng/L (48–326) (1–<4-month-olds) to 113.5 ng/L (42.4–278) (4–<8-month-olds) to 91.7 (34–281) ng/L (8–<112-month-olds). In the treatment-experienced group, the median (5%–95% range) serum gastrin levels decreased from 182.5 ng/L (53–628) (1–<4-month-olds, n = 36) to 139.0 ng/L (45.75–503.5) (4–<8-month olds, n = 40) to 101.5 ng/L (48–305) (8–<12-month-olds, n = 22). Statistically significant differences in the baseline serum gastrin between treatment-naïve versus the treatment-experienced groups were seen particularly in the

TABLE 1. Mean dose (mg · kg^{-1} · day^{-1}) of previous H_2-receptor antagonists and proton pump inhibitors

Standardized medication name	N	Mean	Minimum	Maximum	Median	SD
H_2-receptor antagonist						
Pepcid/famotidine	2	1.12	0.93	1.32	1.12	0.273
Zantac/ranitidine	45	7.59	0.25	50.85	6.71	7.255
Proton pump inhibitor						
Helicid/omeprazole/Prilosec/Zegerid	17	1.18	0.02	4.49	1.04	1.034
Prevacid/lansoprazole	22	2.08	0.72	3.85	2.02	0.847

SD = standard deviation.

1- to<4-month age group ($P = 0.002$), and to a lesser extent in the 4- to<8-month age group ($P = 0.043$), but not in the 8- to<12-month age group.

A comparison between subgroups of infants previously exposed to H_2RAs, PPIs, or both shows that the median (5%–95% range) baseline serum gastrin level was higher but not statistically significantly different in H_2RA-exposed infants (164.5 [51–400] ng/L, n = 56) compared with the PPI-exposed infants (136.0 [38–542] ng/L, n = 31). This unexpected result may have been influenced by the percentage of infants in the 1- to <4-month age group (who have the highest baseline serum gastrin levels) who were exposed to H_2RAs (n = 22/56; 39%) versus the percentage of these youngest infants exposed to PPIs (n = 9/31; 29%). Median baseline serum gastrin was highest for infants previously exposed to both H_2RAs and PPIs (201.0 [92–928] ng/L, n = 11) (Fig. 3). The differences between these subgroups of previously exposed infants, however, were not statistically significant. Figure 4 shows that there was no clear correlation between either the dose of the PPIs to which infants were previously exposed (Fig. 4A) and the baseline serum gastrin levels ($r = 0.30831$) or the dose of H_2RAs to which infants were previously exposed (Fig. 4B) and the baseline serum gastrin level ($r = 0.34741$.).

Table 2 shows baseline (OL baseline) and EOS (DB endpoint) serum gastrin levels in infants from the phase III study who were exposed to rabeprazole 10 mg during the OL period (1–3 weeks), and then randomized to either 5- or 10-mg rabeprazole, or placebo during the 5-week DB period. Infants randomized to both 5- and 10-mg rabeprazole in the DB period had a significant increase in their EOS serum gastrin levels compared with their baseline levels (both $P < 0.001$). Infants randomized to placebo during the DB period showed no significant difference between the EOS and baseline serum gastrin levels ($P = 0.186$). A post hoc analysis to determine whether increases in serum gastrin correlated with the amount of rabeprazole exposure

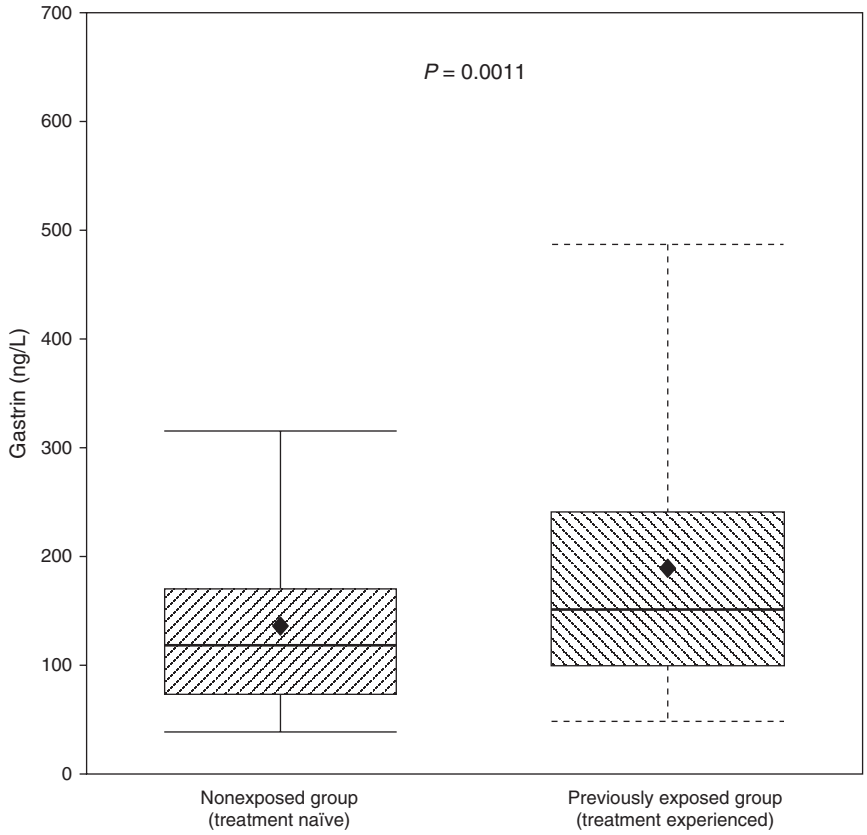

FIGURE 1. Baseline gastrin levels of infants in treatment-experienced (previously exposed) and treatment-naïve (nonexposed) groups.

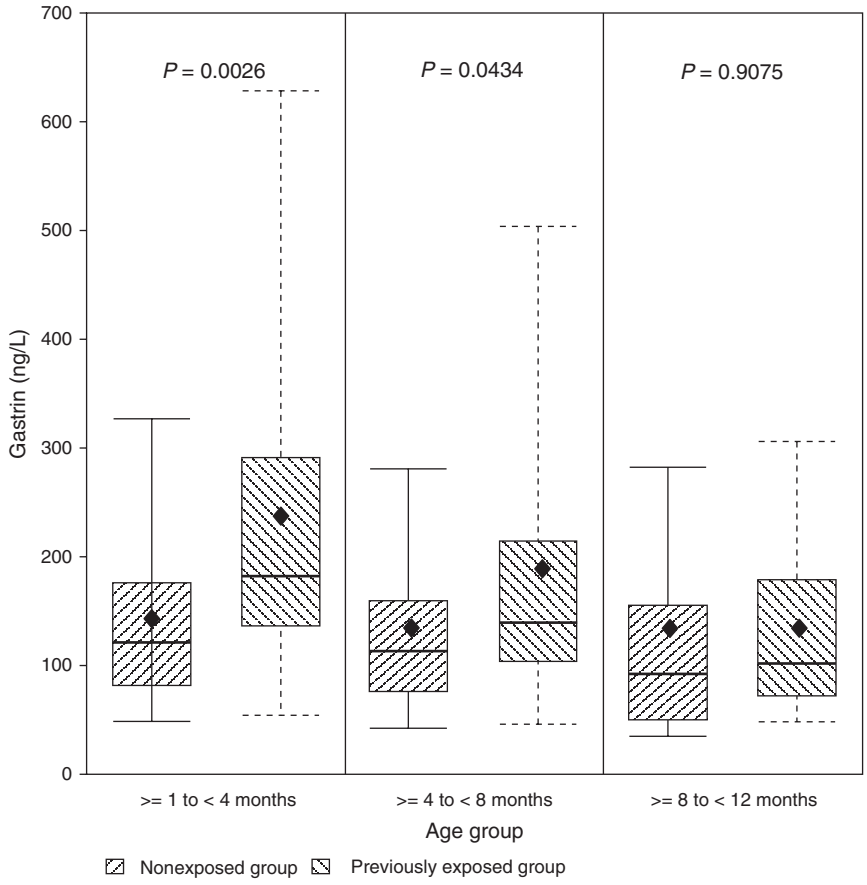

FIGURE 2. Median and 5% to 95% range of baseline serum gastrin in treatment-naïve (nonexposed) versus treatment-experienced (previously exposed) subgroups divided by age.

during the phase III study showed that increases in the EOS serum gastrin levels in the infants randomized to 10-mg rabeprazole during the DB period approached a statistically significant increase compared with those randomized to 5-mg rabeprazole ($P = 0.0501$).

DISCUSSION

In this study, the baseline fasting median serum gastrin level in 251 otherwise healthy 1- to 11-month-old infants with symptomatic GERD who were not previously exposed to acid-suppressive drugs was 118.0 ng/L (5%–95% range 39–315 ng/L), which is higher than the standard adult normal range (generally reported as <100 ng/L) (10). Although infants in the first year of life with symptomatic GERD are not strictly ''controls,'' there is no evidence that elevated serum gastrin levels are associated with GERD in infants. *H pylori* gastritis has been associated with hypergastrinemia in 4- to 5-year-old Irish children (11); however, elevated serum gastrin associated with hypochlorhydria caused by diffuse *H pylori* infection and a decrease in parietal cell mass in the gastric body would be distinctly unusual in children younger than 1 year, especially in the United States and Europe, where most of our study sites were located (12,13). Other causes of elevated serum gastrin such as autoimmune gastritis and Zollinger-Ellison syndrome are rare in childhood and have not been reported in infants younger than 1 year (14). Thus, treatment-naïve infants surveyed in these 2 studies can serve as normal controls to derive a normal range for serum gastrin in this age group. Normal serum gastrin laboratory values in infants younger than 1 year should reflect these values and not be based on adult norms. This is especially true for infants 1 to 8 months of age in which the median serum gastrin is greater than the upper limit of normal in adults. By 8 to <12 months, the median serum gastrin falls within the adult normal range; however, a significant number of infants in this age subgroup have normal gastrin levels >100 ng/L.

Our data show that infant serum gastrin levels generally decrease during the first year of life, but, in general, still remain elevated compared with adult levels even at the end of the first year. Gastrin levels in infants appear to be inversely correlated with levels of gastric acid secretion (5). All infants, including premature infants of 24 weeks' gestational age, are able to maintain a basal gastric pH <4 from the first day of life (15–17). Parietal cell mass is the controlling variable in the production of gastric acid and increases with weight gain and age during infancy. By 6 months of age, maximal acid output measured as milliequivalents per hour per kilogram body weight is at approximately the same level as in older children and adults; however, mean titratable acid in milliequivalents per hour does not reach adult levels until approximately 4 years of age (5).

One limitation of this study was the inability to impose a uniform 8-hour period of fasting before drawing blood for analysis of serum gastrin levels in all infants because of the young age and nutritional/metabolic needs of the youngest infants. Because feeding is known to increase serum gastrin levels, this may have played a role in the elevated levels seen in the youngest infants who, in

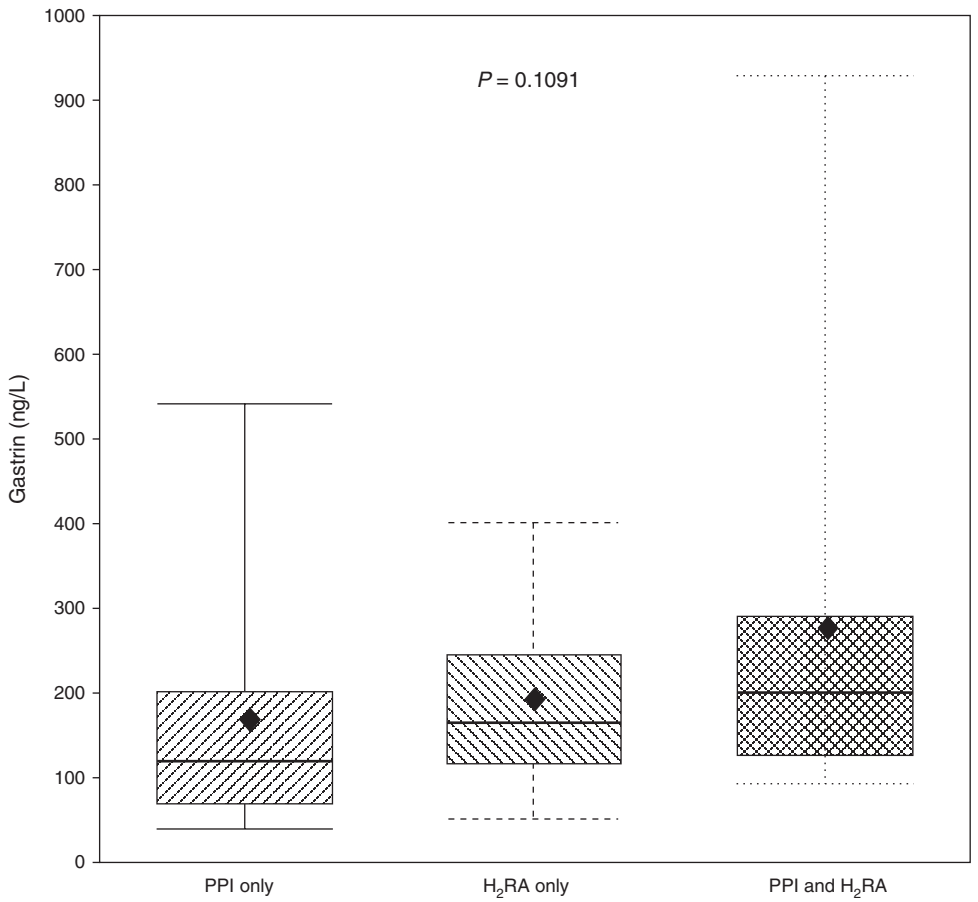

FIGURE 3. Baseline serum gastrin levels in infants previously exposed to proton pump inhibitors, H_2-receptor antagonists, or both.

general, fasted for a shorter time compared with older infants; however, previous data suggest that feeding does not provoke an increase in serum gastrin levels in newborns or infants up to at least 3 months of age (2,3). Thereafter, feeding does seem to stimulate elevations in immediate postprandial serum gastrin levels drawn within 30 minutes of feeding (2). No infant in this study was in the immediate postprandial period because all fasted for at least 3 hours before sampling. In older infants and children, data show that those who fasted for only 4 to 8 hours before blood sampling had a higher serum gastrin level than those who fasted for $\geq$8 hours (18). A shorter duration of fasting may have contributed to the increase in baseline serum gastrin levels in the 4- to <8-month-old age subgroup compared with the 8- to <12-month-old age subgroup; however, these results can still be considered normative because they reflect the limits of fasting that are safe in this age group.

We also did not control for the protein intake in these infants. Some were fed primarily human milk and some primarily formula, which can differ in protein content by a factor of 2 or more. Among many other stimuli, gastrin-releasing peptide neurons, activated by intraluminal protein, stimulate gastrin secretion; however, the effect of intraluminal protein on gastrin secretion is most apparent in the immediate postprandial period, and all of the infants in this study were fasted for at least 3 hours or longer before gastrin sampling. In addition, if protein intake were an important arbiter of serum gastrin levels, one would expect to see higher serum gastrin levels in older infants because they were more likely to have been weaned from breast milk to formula and to have solid baby food incorporated into their meals. The data showed just the opposite. This study was an effort to define a normal range for serum gastrin in both breast-fed and formula-fed infants in their first year of life.

The results from our study support and extend the results of previous smaller studies in newborns and young infants. Newborns have significantly higher concentrations of gastrin in cord venous blood when compared with the maternal levels mainly because of the G34 fraction (2,19). Small studies of infants up to 4 months of age show the maintenance of significantly higher fasting serum gastrin levels in these infants compared with the levels in their mothers' blood (3). In a study of 20 normal newborns, the mean serum gastrin level at 24 hours of age was 66.9 ng/L compared with 44.0 ng/L present in their mothers' blood. The mean fasting serum gastrin levels in these infants at 1, 2, 3, and 4 months, respectively, were 87.3 ng/L, 161.7 ng/L, 82.3 ng/L, and 134.5 ng/L. In a study including a small number of Chinese infants, mean (SD) gastrin values for newborns were higher than adult controls, and this physiologic increase in gastrin levels persisted in the 6-day-old to 6-month-old age group (96.0 [50] ng/L), decreasing to 77.0 (44) ng/L between 7 and 12 months of age (20). A similar Brazilian study that included 11 infants 2 to 6 months of age, 9 children ages 7 to 18 months, and 10 children ages 20 months to 9 years showed that fasting serum gastrin levels were elevated in infants compared with adults and persisted up to 18 months of age, but thereafter approximated normal adult levels (21).

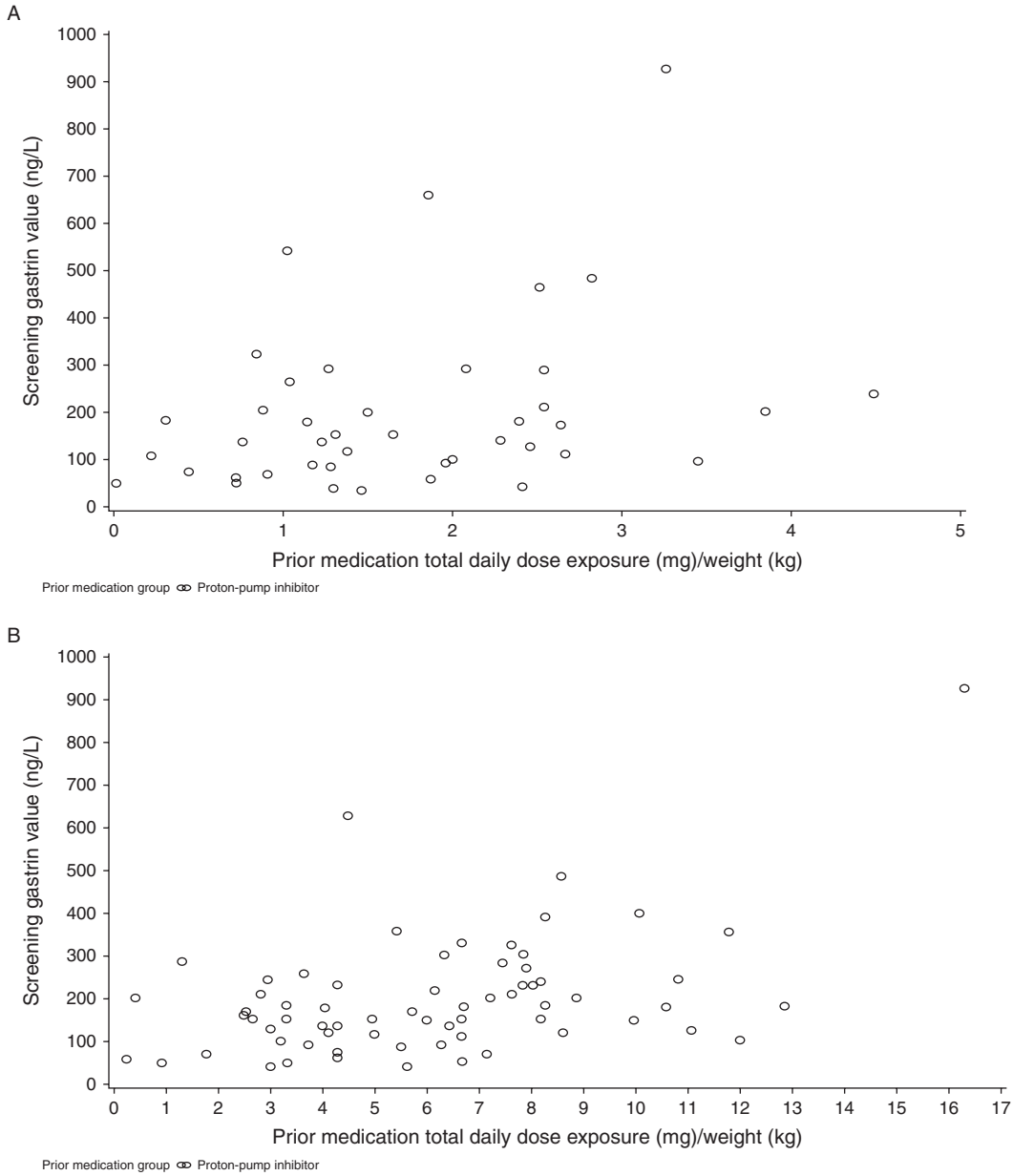

FIGURE 4. Correlation between dose of previous H_2-receptor antagonists or proton pump inhibitors and baseline serum gastrin levels.

In the present study, even relatively short-term exposure to acid-suppressive medication significantly increased serum gastrin levels, particularly in the youngest infants. The median duration of exposure to H_2RAs and PPIs was only approximately 5 weeks before the determination of the baseline fasting serum gastrin level (after a 3-day washout period), but resulted in a statistically significant increase in serum gastrin ($P = 0.0011$), with the bulk of the increase seen in the youngest infants between 1 and 8 months of age. These data suggest that decreased gastric acid secretion, either as a result of reduced parietal cell mass in the first months of life or secondary to pharmacologic suppression or both, is the main driver of hypergastrinemia during the first year.

Higher doses of daily and twice-daily regimens of PPIs are correlated with greater overall reductions in area under the curve of H^+ concentration in adults monitored with continuous intragastric pH probes. More complete reduction in gastric acid secretion would be expected to be associated with more dramatic elevations in serum gastrin levels as long as antral G cells were intact. We were unable to correlate previous uncontrolled prestudy exposure to increased doses of either H_2RAs or PPIs with higher baseline fasting serum gastrin levels (Fig. 4A, 4B); however, during our controlled phase III study, there was a clear distinction between infants maintained on rabeprazole during the DB period and those exposed to rabeprazole during the OL period and then weaned to a placebo during the DB period. Those maintained on rabeprazole clearly showed a significant increase in EOS compared with baseline fasting serum gastrin (Table 2), and those maintained on the same dose of 10 mg during the DB period that they were given during the OL period appeared to have a more dramatic increase than those reduced to a 5-mg daily dose during the DB period.

TABLE 2. Serum gastrin levels in infants exposed to 10-mg rabeprazole during open-label period (1–3 weeks) followed by exposure to either 5- or 10-mg rabeprazole or placebo during double-blind period (5 weeks) of the phase III study

	N	Mean	SD	Median	Minimum	Maximum	*P* (double-blind endpoint vs open-label baseline)
Placebo, N = 89							
Open-label baseline	84	138.45	111.98	117.00	34.3	928.0	0.186
Double-blind endpoint	79	124.52	94.17	94.00	22.4	575.0	
Rabeprazole 5 mg, N = 90							
Open-label baseline	86	147.60	103.62	123.50	34.0	483.0	<0.001
Double-blind endpoint	78	245.39	151.19	227.00	49.0	833.0	
Rabeprazole 10 mg, N = 88							
Open-label baseline	82	179.33	170.07	135.00	19.0	1000.0	<0.001
Double-blind endpoint	75	331.59	221.60	314.00	20.0	1001.0	

SD = standard deviation.

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