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Original article

Combined therapy in gastro-esophageal reflux disease of term neonates resistant to conservative therapy and monotherapy: a clinical trial

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Abstract

Background: Gastroesophageal reflux disease (GERD) is one of the most common problems in neonates. The main clinical manifestations of neonatal GERD are frequent regurgitation or vomiting associated with irritability, crying, anorexia or feeding refusal, failure to thrive, arching of the back and sleep disturbance.

Aims: As no study has compared metoclopramide plus ranitidine with metoclopramide plus omeprazole in the management of neonatal GERD resistant to conservative and monotherapy, this study was carried out.

Study design: This study was a randomized clinical trial of term neonates with GERD resistant to conservative and monotherapy admitted to the neonatal ward of Bahrami Children Hospital during 2013-2015. Totally, 116 term neonates (mean age 10.53 ± 8.17 days; girls 50.9%) were randomly assigned to a double blind trial with either oral omeprazole plus metoclopramide (group A) or oral ranitidine plus metoclopramide (group B). The changes of the symptoms and signs were recorded after one week and one month.

Results: There was no significant difference in demographic and baseline characteristics between the two groups. The response rate of "omeprazole plus metoclopramide" was significantly higher than "ranitidine plus metoclopramide" (93.74% ± 7.28% vs. 75.43% ± 23.24%, p = 0.028). All clinical manifestations recovered significantly in group A while the response rate of irritability and wheezing was not significant in group B (primary outcome). There were no side effects in either group after one week and one month of treatment (secondary outcome).

Conclusions: The response rate was > 70% in each group, but it was significantly higher in group A (> 90%). Combination of each acid suppressant with metoclopramide led to higher response rate in comparison with monotherapy used before intervention.

Keywords

Gastroesophageal reflux disease, neonates, ranitidine, omeprazole, metoclopramide, combined therapy.

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Introduction

Gastro-esophageal reflux (GER), defined as retrograde passage of gastric contents into the esophagus, is a normal physiological process occurring daily in at least 40% of infants [1, 2]. It is most commonly observed during the first 4 months of life. It is being reported in two-thirds of healthy infants and the prevalence decreases gradually to reach one-third in the second 4-month period and almost 4% after the age of 1 year [3].

Conversely, gastro-esophageal reflux disease (GERD), with a prevalence ranging from 8.5% in Eastern Asia to 10-20% in Western Europe and North America, is one of the most common reasons for referrals to pediatricians or pediatric gastroenterologists. It refers to troublesome symptoms or conditions (e.g. frequent vomiting, poor weight gain, irritability and respiratory symptoms) which complicate the physiologic GER [1, 4]. The main clinical manifestations of neonatal GERD are frequent regurgitation or vomiting associated with irritability, crying, anorexia or feeding refusal, failure to thrive, arching of the back and sleep disturbance. It may be associated with respiratory symptoms such as coughing, chocking, wheezing or upper respiratory tract symptoms [5]. Factors such as prematurity, positive family history of GERD, neurological impairment, drugs (e.g. sedatives and muscle relaxants) and malformations of gastrointestinal tract are known to increase the risk of GERD [2].

The main aims of GERD management in infants are to maintain symptomatic relief and adequate growth, and to prevent its recurrence and related complications [6]. Acid suppressants, including Histamine-2 receptor antagonists (H2RAs) and proton pump inhibitors (PPIs) have been increasingly regarded as the mainstay of GERD treatment in pediatrics [1]. According to the recent guidelines, it is recommended to consider a 4-week trial of a PPI or H2RA for infants who present with symptoms such as unexplained feeding difficulties, distressed behavior and weight gain difficulties in addition to overt regurgitation [2].

PPIs (e.g. omeprazole) act through irreversible inactivation of H+/K+-ATPase in the gastric parietal cells canaliculi, leading to inhibition of gastric acid production, decrease total volume of gastric secretion and facilitation of gastric emptying [7, 8]. The longer duration of action of PPIs, inhibition of meal-induced acid secretion and fewer complications have contributed to their superiority over H2RAs that decrease acid secretion by inhibiting H2 receptors on gastric parietal cells [4]. Furthermore, tachyphylaxis may develop after repeated administration of H2RAs, resulting in a decline in acid suppression [9].

According to a study by Cucchiara, a standard dose of omeprazole is comparable with a high dose of ranitidine in symptomatic relief and healing of esophagitis in children [10]. There are still controversies about the management of neonatal GERD. To the best of our knowledge, few clinical trials have compared the effectiveness of PPIs and H2RAs in pediatric GERD, especially in neonates and infants [11]. As there is no study to compare metoclopramide plus ranitidine with metoclopramide plus omeprazole in the management of neonatal GERD resistant to conservative therapy and monotherapy, this study was carried out.

Methods

In the present double-blind randomized controlled trial, we compared the effectiveness of metoclopramide + omeprazole and metoclopramide + ranitidine in the management of symptomatic neonatal GERD. The number of participants was determined by a prospective power analysis, assuming a power of at least 80%, a 2-sided alpha of 0.05 and a positive treatment response in 84% of the metoclopramide + omeprazole group and 63% of the metoclopramide + ranitidine group, based on the study by Cucchiara et al. [10].

One hundred and sixteen term neonates, who were diagnosed with GERD in neonatal ward of Bahrami Children Hospital during 2013-2015, were enrolled. The study protocol was approved by the Research Ethics Committee of Tehran University of Medical Sciences (IR.TUMS.1393.110 code). Written informed consent was obtained from parents or guardians of all infants before enrollment.

Subjects

Term neonates, aged < 30 days, with the diagnosis of clinical GERD and a response rate of < 50% to conservative therapy (anti GERD position, reduction of the feeding volume while increasing the frequency of feedings, use of thickeners and hypoallergenic formulas or encouraging mothers to use hypoallergenic regimen) and monotherapy with metoclopramide, ranitidine or omeprazole alone were included in the study.

The term neonates with any underlying condition for GERD (e.g. gastrointestinal anomalies, neurological disorders, usage of any relaxant or sedative medications) were excluded from the study.

The diagnosis was made by the attending neonatologist clinically if any term newborn had frequent regurgitation or vomiting associated with irritability, crying, anorexia or feeding refusal, failure to thrive, arching of the back and sleep disturbances or symptoms such as coughing, chocking, wheezing or upper respiratory tract symptoms while other etiologies for the clinical presentations such as gastrointestinal obstruction, increased intracranial pressure, meningitis, etc. were ruled out.

Treatment

A random allocation sequence was generated by an independent statistician. Neonates who met the inclusion and exclusion criteria were randomly assigned (in blocks of two per site) to a double blind therapeutic trial with either oral omeprazole (0.5 mg/kg/dose, twice daily) plus oral metoclopramide or oral ranitidine (2 mg/kg/dose, three times daily) plus oral metoclopramide. Metoclopramide was administered at a dose of 0.15 mg/kg/dose three times daily in both groups.

Before initiation of pharmacotherapy, a checklist was filled by the parents/guardians of each participant, including demographic data (age, gender, birth weight, weight at presentation) and symptoms attributed to GERD. After one week of treatment, the patients were re-evaluated by the same neonatologist who had made the primary diagnosis and their post-treatment weight and changes in symptoms were recorded.

Changes of GERD-related symptoms and signs from baseline to the end of treatment were considered as the primary outcome and complications of ranitidine, omeprazole and metoclopramide were defined as the secondary outcome.

Data analysis

Data are presented as mean and standard deviation (SD). Post-treatment results were compared with baseline data using a two-sided paired t test for differences in means and chi-square test and Fisher's exact test (two-sided) for differences in the percentage of patients' responses to treatment. P-values less than 0.05 were considered significant.

Results

In this double-blind randomized controlled trial, 116 term newborns (mean age: 10.53 ± 8.17 days, range: 1-29 days, girls: 50.9%) were enrolled. The mean birth weight of the study subjects was 3,057.84 ± 421.76 g, and only 11 (9.4%) of them had a birth weight of < 2,500 g. There was a positive history of parental GERD in 38 (32.8%) cases. All participants were evaluated by the attending neonatologist and diagnosed with GERD based on the clinical criteria. The neonates were randomized to receive metoclopramide + ranitidine (n = 58, ranitidine was administered at a dose of 2 mg/kg/dose three times daily) or metoclopramide + omeprazole (n = 58, omeprazole was administered at a dose of 0.5 mg/kg/dose twice daily).

There was no significant difference in demographic data and baseline characteristics between the two groups (**Tab. 1**). The participants of both groups were fed by breast-milk plus rice cereal or antireflux formula. The frequency of feeding was every two hours.

The most frequent gastrointestinal-related signs and symptoms were regurgitation, rumination, and vomiting, while the most frequent respiratory-related signs and symptoms were wheezing, coughing, apnea and cyanosis. No cases of hematemesis, anemia, or stridor were reported (**Tab. 2**).

Table 1. Demographic and baseline characteristics of study groups.

Patients' characteristics	Metoclopramide + omeprazole (n = 58)	Metoclopramide + ranitidine (n = 58)	p-value
Gender			
Girls, n (%)	29 (50%)	30 (51.7%)	0.853
Boys, n (%)	29 (50%)	28 (48.3%)	
Age, mean ± SD, days	10.2 ± 7.29	10.98 ± 8.6	0.518
Birth weight, mean ± SD, g	3,056.00 ± 410.77	3,059.69 ± 435.95	0.7
Weight at presentation, mean ± SD, g	3,025.86 ± 394.26	3,054.83 ± 438.05	0.888
Mother's level of education			
Illiterate	-	1 (1.7%)	0.836
Diploma	41 (70.7%)	42 (72.4%)	
Masters and above	17 (29.3%)	15 (25.9%)	
Positive family history of GERD, n (%)	19 (32.8%)	19 (32.8%)	1.000

GERD: gastroesophageal reflux disease.

Table 2. GERD-related signs and symptoms before and after one week of intervention (continues on the next page).

Clinical manifestations	Metoclopramide + omeprazole (n = 58)	Metoclopramide + ranitidine (n = 58)	Inter-group [b] p-value
Irritability, n (%)			
Baseline	30 (51.7%)	32 (55.2%)	
Post-treatment	4 (6.9%)	15 (25.9%)	0.003
Response rate	86.6%	53.1%	
Intra-group p-value [a]	0.002	0.06	
Regurgitation, n (%)			
Baseline	54 (93.1%)	53 (91.3%)	
Post-treatment	4 (6.9%)	14 (24.1%)	0.04
Response rate	92.5%	73.5%	
Intra-group p-value [a]	0.001	0.03	
Vomiting, n (%)			
Baseline	40 (68.9%)	42 (72.4%)	
Post-treatment	3 (5.2%)	10 (17.2%)	0.03
Response rate	92.5%	76.1%	
Intra-group p-value [a]	0.017	0.04	
Rumination, n (%)			
Baseline	31 (53.4%)	29 (50%)	
Post-treatment	7 (12.06%)	18 (31.0%)	0.011
Response rate	77.4%	37.9%	
Intra-group p-value [a]	0.008	0.000	
Sleep disturbance, n (%)			
Baseline	1 (1.7%)	3 (5.2%)	
Post-treatment	0 (0%)	0 (0%)	0.12
Response rate	100%	100%	
Intra-group p-value [a]	0.000	0.000	
Failure to thrive, n (%)			
Baseline	3 (5.2%)	3 (5.2%)	
Post-treatment	0 (0%)	0 (0%)	0.34
Response rate	100%	100%	
Intra-group p-value [a]	0.000	0.000	
Coughing, n (%)			
Baseline	10 (17.2%)	4 (6.9%)	
Post-treatment	1 (1.7%)	1 (1.7%)	0.000
Response rate	90%	75%	
Intra-group p-value [a]	0.017	0.03	

Table 2. GERD-related signs and symptoms before and after one week of intervention (continues from the previous page).

Clinical manifestations	Metoclopramide + omeprazole (n = 58)	Metoclopramide + ranitidine (n = 58)	Inter-group [b] p-value
Wheezing, n (%)			
Baseline	15 (25.9%)	14 (24.1%)	
Post-treatment	1 (1.7%)	8 (13.8%)	0.03
Response rate	93.3%	42.8%	
Intra-group p-value [a]	0.005	0.09	
Apnea, n (%)			
Baseline	8 (13.8%)	7 (12.1%)	
Post-treatment	0 (1.7%)	2 (3.4%)	0.000
Response rate	100%	71.4%	
Intra-group p-value [a]	0.000	0.000	
Milk spilling out of nose, n (%)			
Baseline	4 (6.9%)	5 (8.6%)	
Post-treatment	0 (0%)	0 (0%)	0.15
Response rate	100%	100%	
Intra-group p-value [a]	0.000	0.000	
Cyanosis, n (%)			
Baseline	8 (13.8%)	7 (12.1%)	
Post-treatment	0 (0%)	0 (0%)	0.72
Response rate	100%	100%	
Intra-group p-value [a]	0.012	0.006	
Overall response rate, mean ± SD	93.74% ± 7.28%	75.43% ± 23.24%	0.028

[a] Intra-group p-value means p-value between pre- and post-intervention in every group; [b] inter-group p-value means p-value between two groups of intervention.

The comparison of baseline and post-treatment GERD-associated clinical manifestations categorized by the treatment group are presented in **Tab. 2**. The total response rate following treatment with omeprazole plus metoclopramide was significant in comparison with ranitidine plus metoclopramide (93.74% ± 7.28% vs 75.43% ± 23.24%, p = 0.028). All clinical manifestations improved significantly in omeprazole plus metoclopramide group while the response rate of irritability and wheezing was not significant in the ranitidine plus metoclopramide group (intra-group comparison). The response rate of failure to thrive, sleep disturbance, milk spilling out of nose and cyanosis was 100% in both groups, so the p-values between these four clinical presentations were not significant in two groups (inter-group comparison). The response rate after one month was the same as the response rate after one week in both groups (**Tab. 2**).

Discussion

The present randomized clinical trial study was conducted to compare the effectiveness of oral ranitidine plus metoclopramide with oral omeprazole plus metoclopramide in the treatment of neonatal GERD resistant to conservative therapy and monotherapy. To the best of our knowledge, few clinical trials have compared the effectiveness of PPIs and H2RAs in pediatric GERD, especially in neonates and infants [11]. In this study, 116 subjects were randomly selected, allocating 58 neonates to each group. This study sample was larger than most of the previous studies that were performed in 10-50 infants [12-14].

Oral PPIs have been increasingly used in children < 12 months of age for treatment of GERD during the last few years worldwide. According to a cohort study of US infants aged 0-12 months, PPI prescriptions increased by a factor of 7.5 from 1999 to 2004 and PPI initiated pediatric patients increased from 31.5% in 1999 to 62.6% in 2005 [15, 16]. Acting through inhibition of gastric acid secretion by blocking the enzyme H+/K+-ATPase regardless of the stimulus for acid production, PPIs have gained a widespread popularity leading to 30% less discontinuation and 90% less therapy switch in the first month [7, 16, 17]. Despite the information presented above, PPIs have been rarely used in infants and neonates as the first-line therapy for treatment of GERD due to

few comparative studies versus H2 blockers. The current approach to the management of GERD in infants requiring acid suppression treatment is "step-up" therapy, which is initiating ranitidine at standard dosages and switching to omeprazole if the symptoms persist despite administration of high dose ranitidine [18].

Recent data have demonstrated that the majority of symptoms in neonatal GERD are associated either with non-acid reflux or with no reflux at all [19]. Although studies have also showed no association between GERD and cardiorespiratory events, including apnea, bradycardia, and oxygen desaturation in preterm infants [20, 21], 75% of the neonatologists have reported using GERD medications to treat apneas [14].

Several studies have shown that H2RAs/PPIs are frequently used in neonates in the USA and even continued to discharge, despite a lack of published evidence for improved outcomes following their administration [22-26] and increasing concerns for adverse effects [1, 27, 28].

Slaughter et al. [29] reported that the highest frequency of PPI treatment was seen in extremely-preterm infants and the majority of patients remained on treatment at discharge. They also showed that H2RAs/PPIs were most often initiated for premature infants at a median postmenstrual age of 33-34 weeks when they could tolerate near normal oral feeding.

However, the pharmacokinetics of PPIs is thought to be age-dependent in the pediatric population. A study of the age-dependent pharmacokinetics of lansoprazole in neonates and infants indicated that neonates require a lower dose to achieve similar plasma exposure [30]. According to Bishop et al., omeprazole at a dose of 0.7-2.8 mg/kg/day is effective for treatment of GERD in children younger than 2 years [31]. In the present study, omeprazole was administered at a dose of 1 mg/kg/day.

Although the total response rate in each group was > 70%, our findings showed that the response rate was significantly higher in the omeprazole group than the ranitidine group (93.74% ± 7.28% vs. 75.43% ± 23.24%, p = 0.028). Treatment with omeprazole plus metoclopramide improved all clinical manifestations significantly while the response rate of irritability and wheezing was not significant in the ranitidine plus metoclopramide group.

The difference between the results of our study and other investigations might be due to several factors. First, the response to treatment in each group was evaluated by reduction or elimination of symptoms and signs, which is in contrast to other reports that have used changes in clinical manifestations with or without pH and/or endoscopic changes as the criteria for effectiveness of pharmacological measures. On the other hand, only full-term healthy neonates aged < 1 month were enrolled in our study. In other words, preterm infants, those with disorders predisposing to GERD (such as gastrointestinal anomalies, neuromuscular diseases, and respiratory distress), and neonates admitted to NICU were excluded from the study.

In the present study, a combination of an acid suppressant with metoclopramide led to a higher response rate in comparison with monotherapy used before the intervention. It seems that the synergistic effect of an acid suppressant in combination with metoclopramide on the lower esophageal sphincter led to a higher response rate in these patients in comparison with their previous treatment, i.e. monotherapy with an acid suppressant or prokinetic agent alone.

There is increasing evidence that acid suppressants may be harmful in infants and children, especially those with immune deficiency or with indwelling catheters. They can induce lower respiratory tract infections, gastroenteritis, and candidal infection [28]. They may also increase the risk of necrotizing enterocolitis, nosocomial infections, and mortality in premature infants [32, 33]. According to Kierkus et al. [34], PPIs are well tolerated in short-term use and are associated with mild to moderate side effects. However, more research is needed to determine their efficacy and safety in children below one year of age [16].

Metoclopramide is an antagonist of the dopamine D2 receptor subtype. A systematic review of metoclopramide therapy for GERD in infants found insufficient evidence for either efficacy or safety in this population [35]. Reported complications of metoclopramide in infants include irritability, drowsiness, oculogyric crisis, dystonic reaction, apnea and emesis [35]. On the other hand, FDA in 2009 reported that tardive dyskinesia is induced with prolonged or high-dose metoclopramide exposure [36], so tardive dyskinesia is rare with short-duration or low-dose metoclopramide administration. We observed no side effects for medications used in each group.

Similar studies with more participants in this age group are required to determine the efficacy of combined therapy in neonatal GERD.

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Declaration of interest

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References

1. Vandenplas Y, Rudolph CD, Di Lorenzo C, Hassall E, Liptak G, Mazur L, Sondheimer J, Staiano A, Thomson M, Veereman-Wauters G, Wenzl TG, North American Society for Pediatric Gastroenterology Hepatology and Nutrition, European Society for Pediatric Gastroenterology Hepatology and Nutrition. Pediatric gastroesophageal reflux clinical practice guidelines: joint recommendations of the North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition (NASPGHAN) and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition (ESPGHAN). J Pediatr Gastroenterol Nutr. 2009;49(4):498-547.
2. National Collaborating Centre for Women's and Children's Health, Gastro-oesophageal reflux disease: recognition, diagnosis and management in children and young people (NICE guideline, No. 1). London (UK): National Institute for Health and Care Excellence (NICE), 2015.
3. Hegar B, Dewanti NR, Kadim M, Alatas S, Firmansyah A, Vandenplas Y. Natural evolution of regurgitation in healthy infants. Acta Paediatr. 2009;98(7):1189-93.
4. Lightdale JR, Gremse DA. Section on gastroenterology, hepatology, and nutrition. Gastroesophageal Reflux. Management guidance for the pediatrician. J Pediatrics. 2013;131(5):e1684-95.
5. Practice Guidelines: AAP Releases Guideline for the Management of Gastroesophageal Reflux in Children. Am Fam Physician. 2014;89(5):395-7.
6. Ferreira CT, Carvalho Ed, Sdepanian VL, Morais MB, Vieira MC, Silva LR. Gastroesophageal reflux disease: exaggerations, evidence and clinical practice. J Pediatr (Rio J). 2014;90(2):105-18.
7. Ward RM, Kearns GL. Proton Pump Inhibitors in Pediatrics. Mechanism of Action, Pharmacokinetics, Pharmacogenetics, and Pharmacodynamics. Pediatr Drugs. 2013;15(2):119-31.
8. Tighe M, Afzal NA, Bevan A, Hayen A, Munro A, Beattie RM. Pharmacological treatment of children with gastro-esophageal reflux. Cochrane Database Syst Rev. 2014;(11):CD008550.
9. Salvatore S, Hauser B, Salvatoni A, Vandenplas Y. Oral ranitidine and duration of gastric pH>4.0 in infants with persisting reflux symptoms. Acta Paediatr. 2006;95(2):176-8.
10. Cucchiara S, Minella R, Iervolino C, Franco MT, Campanozzi A, Franceschi M, D'Armiento F, Auricchio S. Omeprazole and high dose ranitidine in the treatment of refractory reflux oesophagitis. Arch Dis Child. 1993;69(6):655-9.
11. AztraZeneca. AstraZeneca's review of actual PPI use in the treatment of infants with GERD. Briefing Document for the Gastrointestinal Drugs Advisory Committee Meeting November 5, 2010: Clinical Experience Related to the Esomeprazole Clinical Studies in Patients <1 Year of Age with Gastroesophageal Reflux Disease. Available at: https://wayback.archive-it.org/7993/20170404152526/https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/Drugs/GastrointestinalDrugsAdvisoryCommittee/UCM232029.pdf, last access: January 2018.
12. Moore DJ, Tao BS, Lines DR, Hirte C, Heddle ML, Davidson GP. Double-blind placebo controlled trial of omeprazole in irritable infants with gastroesophageal reflux. J Pediatr. 2003;143(2):219-23.
13. Omari TI, Davidson GP, Bondarov P, Naucler E, Nilsson C, Lundborg P. Pharmacokinetics and acid-suppressive effects of esomeprazole in infants 1-24 months old with symptoms of gastroesophageal reflux disease. J Pediatr Gastroenterol Nutr. 2007;45(5):530-7.
14. Omari TI, Haslam RR, Lundborg P, Davidson GP. Effect of omeprazole on acid gastroesophageal reflux and gastric acidity in preterm infants with pathological acid reflux. J Pediatr Gastroenterol Nutr. 2007;44(1):41-4.
15. Nelson SP, Kothari S, Wu EQ, Beaulieu N, McHale JM, Dabbous OH. Pediatric gastroesophageal reflux disease and acid-related conditions: trends in incidence of diagnosis and acid suppression therapy. J Med Econ. 2009;12(4):348-55.
16. Barron JJ, Tan H, Spalding J, Bakst AW, Singer J. Proton pump inhibitor utilization patterns in infants. J Pediatr Gastroenterol Nutr. 2007;45(4):421-7.
17. Marchetti F, Gerarduzzi T, Ventura A. Proton pump inhibitors in children: a review. Dig Liver Dis. 2003;35(10):738-46.
18. Hassall E. Step-Up and Step-Down Approaches to Treatment of Gastroesophageal Reflux Disease in Children. Curr Gastroenterol Rep. 2008;10(3):324-31.
19. Orenstein SR. Infant GERD: symptoms, reflux episodes & reflux disease, acid & non-acid reflux – implications for treatment with PPIs. Curr Gastroenterol Rep. 2013;15(11):353.
20. Di Fiore J, Arko M, Herynk B, Martin R, Hibbs AM. Characterization of cardiorespiratory events following gastroesophageal reflux in preterm infants. J Perinatol. 2010;30(10):683-7.
21. Smits MJ, van Wijk MP, Langendam MW, Benninga MA, Tabbers MM. Association between gastroesophageal reflux and pathologic apneas in infants: a systematic review. Neurogastroenterol Motil. 2014;26(11):1527-38.
22. Davidson G, Wenzl TG, Thomson M, Omari T, Barker P, Lundborg P, Illueca M. Efficacy and safety of once-daily

esomeprazole for the treatment of gastroesophageal reflux disease in neonatal patients. J Pediatr. 2013;163(3):692-8.e1-2.

23. Poets CF. Gastroesophageal reflux: a critical review of its role in preterm infants. Pediatrics. 2004;113(2):e128-32.
24. Rudolph CD. Are proton pump inhibitors indicated for the treatment of gastroesophageal reflux in infants and children? J Pediatr Gastroenterol Nutr. 2003;37(Suppl 1):S60-4.
25. van der Pol RJ, Smits MJ, van Wijk MP, Omari TI, Tabbers MM, Benninga MA. Efficacy of proton-pump inhibitors in children with gastroesophageal reflux disease: a systematic review. Pediatrics. 2011;127(5):925-35.
26. van der Pol R, Langendam M, Benninga M, van Wijk M, Tabbers M. Efficacy and safety of histamine-2 receptor antagonists. JAMA Pediatr. 2014;168(10):947-54.
27. Chen IL, Gao WY, Johnson AP, Niak A, Troiani J, Korvick J, Snow N, Estes K, Taylor A, Griebel D. Proton pump inhibitor use in infants: FDA reviewer experience. J Pediatr Gastroenterol Nutr. 2012;54(1):8-14.
28. Cohen S, Bueno de Mesquita M, Mimouni FB. Adverse effects reported in the use of gastroesophageal reflux disease treatments in children: a 10 years literature review. Br J Clin Pharmacol. 2015;80(2):200-8.
29. Slaughter JL, Stenger MR, Reagan PB, Jadcherla SR. Neonatal H2-Receptor antagonist and proton pump inhibitor treatment at us children's hospitals. J Pediatr. 2016;174:63-70.e3.
30. Zhang W, Kukulka M, Witt G, Sutkowski- Markmann D, North J, Atkinson S. Age-dependent pharmacokinetics of lansoprazole in neonates and infants. Paediatr Drugs. 2008;10(4): 265-74.
31. Bishop J, Furman M, Thomson M. Omeprazole for Gastroesophageal Reflux Disease in the First 2 Years of Life: A Dose-finding Study with Dual-channel pH Monitoring. J Pediatr Gastroenterol Nutr. 2007;45(1):50-5.
32. Terrin G, Passariello A, De Curtis M, Manguso F, Salvia G, Lega L, Messina F, Paludetto R, Canani RB. Ranitidine is associated with infections, necrotizing enterocolitis, and fatal outcome in newborns. Pediatrics. 2012;129(1):e40-5.
33. Santana RNS, Santos VS, Ribeiro-Júnior RF, Freire MS, Menezes MAS, Cipolotti R, Gurgel RQ. Use of ranitidine is associated with infections in newborns hospitalized in a neonatal intensive care unit: a cohort study. BMC Infect Dis. 2017;17(1):375.
34. Kierkus J, Oracz G, Korczowski B, Szymanska E, Wiernicka A, Woynarowski M. Comparative safety and efficacy of proton pump inhibitors in paediatric gastroesophageal reflux disease. Drug Saf. 2014;37(5):309-16.
35. Hibbs AM, Lorch SA. Metoclopramide for the treatment of gastroesophageal reflux disease in infants: a systematic review. Pediatrics. 2006;118(2):746-52.
36. US Food and Drug Administration. Metoclopramide-containing drugs. Available at: http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm106942.htm, date of publication: 2009, last access: November 7, 2013.