Proton Pump Inhibitors Therapy in Children with Gastroesophageal Reflux

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ABSTRACT

Proton pump inhibitors (PPI) has been widely used by clinicians to treat diseases that require suppression of gastric acid. PPI work by inhibiting the proton pump in gastric parietal cells.In adult patients, PPI has been widely studied and showed effective results and safe. This result make PPI positioning as the first choice medicine in the treatment of diseases that require suppression of gastric acid. As the primary choice therapy, PPI administration has been increased not only in adults but also in children.

PPI is often administered to children with a diagnosis of gastroesophageal reflux disease (GERD) which defined as symptoms or complications caused by gastroesophageal reflux (GER). GERD diagnosis in children is quite difficult, so it is common to find that diagnosis is established only by the basis of clinical symptoms, resulting in overdiagnosis and over-treatment of GERD. The use of PPI in children still needs further study and can not be inferred based on adult studies. Inappropropriate PPI prescription without indication will increase side effect, risk and also harm the children. Thus, it is important to know the indications, side effects and safety of PPI therapy in children.

Keywords: *proton pump inhibitor, children, gastroesophageal reflux disease*

ABSTRAK

Penghambat pompa proton (PPP) telah banyak digunakan oleh klinisi untuk mengobati penyakit yang membutuhkan supresi asam lambung. PPP bekerja dengan cara menghambat pompa proton pada sel parietal lambung. PPP sudah banyak diteliti pada dewasa dan menunjukan hasil yang efektif dan aman. Hasil ini membuat PPP menjadi pilihan utama pada penyakit yang memerlukan supresi asam lambung. Terapi PPP sebagai pilihan utama telah meningkatkan pemberian PPP tidak hanya pada dewasa tetapi juga pada anak.

PPP sering diberikan kepada anak dengan diagnosis penyakit refluks gastroesofagus (PRGE) yang didefinisikan sebagai gejala atau komplikasi yang diakibatkan oleh refluks gastroesofagus (RGE). Diagnosis PRGE pada anak cukup sulit, sehingga tidak jarang diagnosis ditegakkan hanya berdasarkan gejala klinis yang berujung pada overdiagnosis dan over-treatment PRGE. Penggunaan PPP pada anak masih memerlukan penelitian lebih lanjut dan tidak dapat disimpulkan berdasarkan penelitian pada dewasa. Pemberian PPP yang tidak sesuai indikasi akan meningkatkan resiko terjadinya efek samping dan dapat membahayakan. Melihat hal ini maka penting untuk mengetahui indikasi, efek samping dan keamanan terapi PPP pada anak.

Kata kunci: *penghambat pompa proton, anak, penyakit refluks gastroesofagus*

INTRODUCTION

Proton pump inhibitors (PPI) have been prescribed many times since 1999 and also increased in children rapidly.[1-5] PPI are drugs that used to suppress acid production by inhibiting proton pump in parietal cell. PPI therapy has been widely studied in adult, and showed that PPI has good efficacy and safety in the treatment of diseases that require suppression of acid

production.[6-9] However, PPI therapy in children led to many debate related to the indications, characteristics of children who benefit from PPI therapy, the efficacy, and safety in children.

PPI is often given to children as empirical therapy or before gastroesophageal reflux disease (GERD) diagnosis is confirmed. Diagnosis most often based on clinical symptom such as refusing to eat, unexplained crying, irritable, or regurgitation.[10,11] Unexplained crying or irritability are the most common symptoms that clinician took as the basis to diagnosis GERD and prescribe PPI, even though these have made overdiagnosis of GERD in children.[4,5] There is no proof that unexplained crying in children is caused by pain in abdomen or any part of their body; it is likely a phenomenon of normal development in children. Many gastrointestinal symptoms are not caused by gastroesophageal reflux (GER) but other disease or cause such as sensitivity to milk or dietary protein, urinary tract infection or other infection.[4,5]

Diagnosing GERD or prescribing PPI to children is the last thing to do, rather clinician should take complete history of children, discussing behavioural and dietary consumption, giving explanation and reassurace to caregiver or parents before prescribing PPI even those thing are time consuming. Children with benign and self resolving symptom such as spitting up, regurgitation, or unexplained crying in a heathy infant cannot be easily diagnose as GERD and do not warrant PPI as a therapy.[5] Seeing this, empirical therapy of PPI can't be easily justified if not based on careful diagnosis and consideration because PPI itself has side effect. If PPI is not clinically proven effective in children then it shouldn't be given.[11] This review tend to explain GERD in children as a diagnosis and which children will be having benefit from PPI therapy, also the benefit and risk of prescribing PPI in children.

GASTROESOPHAGEAL REFLUX DISEASE

Gastroesophageal reflux disease (GERD) is defined when gastroesophageal reflux (GER) cause reflux symptoms and complications. Gastroesophageal reflux itself is defined as passive movement of gastric content into esophagus involuntarly.[12-16] GERD is often encountered in infant and children. A study in 2009 at United States showed a prevalence of 12.4% in infants and 1% in the other pediatric age group.[17] GER is not a pathologic processes when there is no disturbing symptoms or complication.[12-16] A multicenter study conducted in children aged 3-17 years showed the prevalence of GER symptoms was 1.8-7.2% in children aged 3-9 years and 5-8.2% in children aged 10-17 years, but another study said that it was difficult to measure GER prevalence accurately.[16,18]

Study in Indonesia conducted by Hegar et al showed regurgitation peak occurred at 4 months of age (68.6%) and decreased (35.7%) at the age of 4-8 months. The study also stated that the Indonesian infants rarely experienced regurgitation more than four times a day after 8 months of age. Further study in Indonesia by Hegar et al showed that regurgitation occurs after the age of 6 months will drop significantly in the next 3 months. This study also stated that GERD is a rare occurrence and it is supported by the findings that only 1/137 infants were diagnosed with GERD.[19,20]

Table 1. Symptom and sign that maybe associated with gastroesophageal reflux[10]

Symptoms	Signs
Recurrent regurgitation with/ without vomitting	Esophagitis
Weight loss or poor weight gain	Esophageal stricture
Irritability in infants	Barrett's esophagus
Ruminative behaviour	Laryngeal/pharyngeal inflammation
Heartburn or chest pain	Recurrent pneumonia
Hematemesis	Anemia
Dysphagia, odynophagia	Dental erosion
Wheezing	Feeding refusal
Stridor	Dystonic neck posturing (Sandifer syndrome)
Cough	Apnea spells
Hoarseness	Apparent life-threatening events

Excellent history taking and physical examination must be done before we do a diagnostic test especially an invasive one such as endoscopy and biopsy was done. Complete history will help in diagnosis process and therapy. GERD symptoms and signs are important thing we must know as a clinician because these are the entry point to diagnose children with GERD as we can see in Table 1. When children with GERD symptoms and signs have a warning sign (Table 2), then a complete work up and differential diagnosis must be done. After the diagnosis is confirmed, therapy can be administered to the children without delay.[10]

Diagnosing GERD is often difficult because there is no golden standard and many patients received therapy empirically before the diagnosis is confirmed.[10,11] GERD is often diagnosed based solely on the present of disturbing clinical symptoms in children.[10,11] Examination to support GERD diagnosis such as endoscopy and pH monitoring showed poor sensitivity.[10,11] Histopathology examination also has poor correlation with endoscopy and severity of the symptom. There are 2 studies that prove these, study by Vieira et

Table 2. Warning signal requring investigation in infants with regurgitation or vomitting[10]

Bilious vomitting
Gastrointestinal bleeding
Hematemesis
Hematochezia
Consistently forceful vomitting
Onset of vomitting after 6 months of life
Failure to thrive
Diarrhea
Constipation
Fever
Lethargy
Hepatospelomegaly
Bulging fontalnelle
Macro/microcephaly
Seizures
Abdominal tenderness or distension
Documented or suspected genetic/metabolic syndrome

al in Brazil and Genta et al in US show that although there is an abnormality on endoscopy does not mean there is always also histopathology abnormality and otherwise.[23,24] Despite of its poor sensitivity, endoscopy with Los Angeles (LA) Classification is commonly used to aid the diagnosis of GERD in pediatric.[10]

Many studies try to develop questionnaire, the questionnaire purpose is to quantify the GERD symptom that will help clinician to diagnose GERD. Some of the questionnaire are infant gastroesophageal reflux questionnaire (I-GERQ) by Orenstein in 1996, I-GERQ revised (I-GERQ-R) as the revision from I-GERQ by Kleinman in 2006 and the latest pediatric gastroesophageal reflux disease symptom and quality of life questionnaire (PGSQ-Cp) by Kleinman in 2011.[27] These developed questionnaires also have poor sensitivity and for PGSQ-Cp still need further study.[10,25-27] Therefore, although the diagnosis of GERD is a difficult job to do, the disease still need therapy and delaying treatment can't be justified if the child need it. However, giving the therapy to soon without a proper diagnosis to confirm is not justified either.[11]

PROTON PUMP INHIBITOR

Proton pump inhibitor (PPI) works by inhibiting the H^+K^+ ATPase pump in the gastric parietal cells. PPI should be activated to be able to bind with cysteine on proton pump with the rate of activation is different depending on the structure of each PPI. PPI that binds to cysteine on the pump will form covalent disulfide bonds. When bonds are formed the pump is inactivated and gastric acid secretion is inhibited reversibly or irreversibly. The PPI steady state is achieved within 3 days after the first dose, because not all the pumps are active and blocked on the first dose. PPI should be given before meals because meal will induce gastrin secretion. Gastrin is a potent stimulator of the activation of proton pumps. PPI should be given 1 hour before meals to be absorbed and not eliminated by the time the proton pump is activated.[6-9,28]

Gastric acid secretion remained inhibited for a long time even though the PPI has been eliminated from the circulation. PPI is a weak base and acid labile so it should be given in the form of enteric coating to prevent degradation by stomach acid and allow absorption in the small intestine that have more alkaline environment. PPI is not a dose dependent drug.[6-9,28]

PPI is metabolized by cytochrom P450 with enzymes CYP2C19 and CYP3A4. Both of these enzymes play a major role in the metabolism of PPI especially CYP2C19. The enzymes activity are immature at birth and reach adult activity at the age of 6-12 months after birth. If there is a genetic disorder such as CYP2C19 polymorphisms, the enzymes activity is decreased and PPI clearance will be impaired then the effect of PPI will be prolonged. Liver disorders also cause clearance impairment of PPI because both of the enzymes are predominantly presence in the liver. Long-term PPI therapy has not cause cancer or significant abnormality in pediatric.[6,9,29]

PROTON PUMP INHIBITOR IN CHILDREN

Prescribing PPI in children continue to rise and this is supported by evident from the data in the US that showed an increase in PPI prescription in children by 7 fold in the span of 6 years (1999-2004) and one PPI drugs prescription with liquid preparations increased 16 fold. In addition to the increasing use of PPI, another study showed that approximately 50% of children before the age of 4 months get it and we should see the fact before that PPI metabolism enzymes mature at the age of 6-12 months after birth. Theoretically, the PPI clearance in 50% of children who received PPI therapy before 4 months had a higher risk of toxicity. Seeing this fact, many infants and children get PPI therapy and the prescribing should be based on data that supported by research evidence without forgetting the risks and benefits of therapy.[1-5]

Consensus and guideline by NASPGHAN/EPSGHAN showed that the administration of empirical therapy can be tolerated as long as 2-4 weeks in older children and adolescents. This empirical therapy could also act as a means of diagnostic.[10] However, empirical PPI therapy is not recommended to be given to infants and younger children with GERD symptoms, unexplained crying, refuse to eat, irritable and regurgitation.[10,11] PPI can be given to infants and

adolescents with reflux esophagitis and are superior to alleviate symptoms and heal esophagitis compared to H2 receptors (H2R) antagonist.[9-11] PPI are superior compared to the H2R antagonist because PPI able to maintain gastric pH at 4 or more, prevent the acid secretion triggered by eating, reduce 24-hour intragastric volume, there by reducing reflux material and facilitate gastric emptying.[9-11]

PPI therapy in infants and younger children is not recommended and this is supported by randomized double blind placebo-controlled studies that showed PPI therapy and placebo have similar effects on symptoms improvement despite the inhibition of acid secretion occurred only in the group of PPI. PPI therapy is recommended only when the infant has reflux esophagitis as GERD complication.[10,11,31-33] Esomeprazole has been reported using in infant.[9] Other PPI which have been reported using in children are omeprazole (≥ 1 year), pantoprazole (≥ 5 years), lansoprazole (≥ 1 year), rabeprazole (12-17 years). Omeprazole and esomeprazole have been reported for maintenance therapy of reflux esophagitis in children.[9-11,30,31]

The timing of PPI administrations very important to gain maximum efficacy and effectivity, GER management guidance for pediatrician from American Academy of Pediatric (AAP) recommend to administer PPI ideally approximately 30 minutes before meals and this must be educated to the parent or patient. This recommendation also said that all clinician should recognize that the metabolism of PPI in children have a shorter half life, necessitating a higher per-kilogram dose to achieve a peak serum concentration and area under the curve similar to those in adult.[32]

Eventhough many PPI have been reported using in children as the previous statement but AAP guidance stated that pantoprazole and dexlansoprazole are not indicated for children. PPI dose and formulation are different and many children cannot swallow pills or capsule. This guidance show the dose required and the administration technique: omeprazole (0.7-3.3 mg/kg/day) sprinkle contents of capsule onto soft foods, lansoprazole (0.7-3 mg/kg/day) sprinkle contents of capsule onto soft food or select juices, esomeprazole (0.7-3.3 mg/kg/day) sprinkle contents of capsule onto soft foods and rabeprazole 20 mg daily oral tablet.[32]

Long-term PPI therapy without confirming the diagnosis is not recommended and the use of PPI should be given in the smallest effective dose when acid secretion suppression is required. Hassal et al studied children aged 1-16 years with PPI therapy using omeprazole for 21 months to maintain remission of reflux esophagitis showed that maintenance dose required are more than half the dose needed for healing in 60% patient.[33] Many patients only require once a day dosing, more dosing are indicated in other specific cases.[9-11]

The largest randomized double-blind placebo-controlled studying PPI therapy in children by Orenstein showed that the symptom improvement of PPI administration and placebo in infants with GERD symptoms are identical (54%).[34] However, the consensus of NAPSGHAN/EPSGHAN stated that the study only proves that PPI is not beneficial in infants with GERD symptoms but not proven that the symptoms are due to GERD.[10] Systematic review of studies by van der Pol showed that the PPI are proven to be ineffective in reducing GERD symptoms in infants.[11]

The debate over the use of the therapy also increased because a study suggest that although the use of PPI in older children seemed safe and well tolerated, the evidence of PPI safety in pediatric is still lacking.[11] Study in PPI therapy with placebo-controlled are also lacking.[11] There are 5 PPI studies in infants, only 1 study showed that PPI is more effective compared to hydrolyzed formula, 2 studies showed that PPI are noteffective and 2 studies showed that PPI are equally effective with placebo.[34-36,38,39]

Van der Pol systematic review also includes research in older children and adolescents. The results showed that PPI therapy is equally effective in adolescents when compared with alginate, ranitidine or different dose PPI.[11] Adolescents study also found mild to moderate side effects in 2 studies.[40,41] Reduction of gastric acid in infants and children showed that PPI are more effective than placebo, alginate or ranitidine at 4 studies.[35,36,42,43] The interesting thing is PPI therapy showed no difference in improvement of histopathology parameter compared with ranitidine or alginate at 3 studies.[42-44] PPI therapy shown to reduce GERD symptoms in adolescents and equally effective when compared with controls at 2 studies.[45,46] This systematic review stated that the recommendation in 2009 for PPI therapy in infants and children is less supported by evidence from double-blind randomized clinical study with placebo controls. While in older children and adolescents, the data or the results are taken from research on adult so it should not be use as the basis of recommendations in children and adolescent.[11]

PPI therapy in infants and children is still being debated due to the lack of clinical research which can support

it.[10,11] The parameters that are often used to measure the efficacy of therapy is the questionnaire that had poor sensitivity.[25-27] Endoscopy and histopathology were still being debated when used as a parameter.[10,11,13,16,23] These cause difficulty in proving that the therapy is effective, cases evaluated in the study require GERD specific symptom to evaluate the therapy but it is usually occur when GERD become chronic and it is difficult to find it in infants and young children.[10,11,47]

SAFETY OF PROTON PUMP INHIBITOR IN CHILDREN

Gastric secret acid has its function so that therapy to inhibit gastric acid secretion should be appropriate. Appropriate therapy will provide more benefits than the risks. In general, infants who received PPI therapy showed that side effects are significantly higher compared with the placebo group. Respiratory tract infections are the most common side effect .[34]

Tolia et al study involving 133 pediatric patients aged 0.1-17.6 years with 32-47 month long therapy, found parietal cell hyperplasia (0-16%), increased gastrin (73%) with normal levels of vitamin B12.[48] This study show interesting things that normal gastric histology is more common when therapy is continued for more than 48 months and treated at higher doses.[48]

Omari et al found gastrointestinal symptoms (constipation, diarrhea and vomiting) in children who have esomeprazole therapy (4.16%) for 7 days.[49] Orenstein et al found that the incidence of lower respiratory tract infections was higher in the lansoprazole group compared with placebo at 4 weeks of therapy.[34] Winter et al and Neu et al showed no difference between pantoprazole and placebo groups with laboratory parameters, weight gain, respiratory infections, and worsening of GERD symptoms.[39,50]

Hassall et al showed that 61% of children receive long-term PPI therapy during 10.8 years (median 2.84 years) underwent mild Enterochromaffin-like cell (ECL) hyperplasia but there are no clinical significance. The study also found no atrophic gastritis or carcinoid tumors. Systematic review by van der Pol states that PPI is generally well tolerated but increases susceptibility to acute gastroenteritis, community pneumonia, respiratory tract infections, gastric polyps and bacterial overgrowth.[11,51–54]

PPI therapy in children which is done without confirming diagnosis or empirical therapy without a strong clinical basis can not be justified. This is based on the side effects that can be inflicted on patients, especially in the group of children who need gastric acid to digest food and the absorption of nutrients which require stomach acid. Inhibition of gastric acid that should not be done is increasing the risk of side effects that shouldn't be occur and also increases the risk of impaired growth in children due to acid suppression. Long-term use showed the presence of mild histological changes but showed no growth of carcinoma and may be given when the benefits outweigh the risk.[3-5]

CONCLUSION

There are a lot of debates on PPI therapy in children that require further clinical study to get data on efficacy of PPI therapy in children, especially in infants and young children. Although it still needs further study, data from recent years showed that the majority of patients receiving PPI therapy experienced more side effect compared with placebo, especially in infants. Seeing this, the therapy should be considered wisely by taking into account the indication, benefits, risks and also side effects. Overdiagnosis and over-treatment of GERD with PPI must be avoided. Careful considerations and clinical experience with the professional ethics of physicians, research evidence and diagnostic tools can make PPI therapy more rational, precise and accurate.

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