ORIGINAL ARTICLE

Does Oral Lansoprazole Really Reduce Gastric Acidity in VLBW Premature Neonates?

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SUMMARY

Premature neonates of very low birth weight (VLBW) whose treatment required the use of naso-gastric tube feeding were investigated. 10 infants suspected of having GERD (gastro-esophageal reflux) received oral lansoprazole therapy by tube administration. 9 other infants formed a control group. In the treated group a fasting pH was determined before treatment and again after 7 days treatment. The control group was similarly assessed at an interval of 7 days. Despite acid reduction, the post-treatment pH mean of 1.31 would continue to pose a threat to the esophageal mucosa. The physiology of neonatal acid secretion is discussed to explain these findings.

KEY WORDS:

Preterm neonate/VLBW/ acid gastro esophageal reflux/proton pump inhibitor/omeprazole/ neonatal hyperacidity/neonatal hypergastrinaemia

INTRODUCTION

The infants we studied were all premature and had very low birth weights (VLBW) (<1500gm.) As many as 85% of such infants are known to suffer from episodes of gastro-oesophageal reflux (GER)[1].

When oesophageal disease is present (GERD), more episodes of acid- reflux rather than volume reflux are recorded[2]. Thus episodes of acid reflux has been presumed to be the causative agent and acid-blocking drugs have been increasingly used in recent times[3].

Oral omeprazole in a dose of 0.7 mgm/kgm/day has been shown to reduce gastric acidity in pre-term infants with a mean age of 50 days. Episodes of reflux < pH 4 detected by an oesophageal probe were much reduced compared to cross-over placebo comparison after 7 days treatment. An antacid (Mylanta) was used in both placebo and treated episodes to ensure the stability of omeprazole[4]. Clearly the effect of administered antacid and the buffering effect of retained milk, may have made the pH more alkaline than would be expected from omeprazole alone.

Premature infants are known to have high fasting gastric acidity in the first 10 days after birth[5] with pH levels around 1-2 , 4 hours after a feed[6]. In post-natal life peak natural and stimulated acidity occurs at around 3-4 weeks of age with a gradual fall thereafter[7, 8].

Thus it is logical to suppose that pre-term VLBW infants below the age of 4 weeks would be likely to be particularly hyperacid with frequent acid-reflux episodes and hence worthy of particular study. We have been unable to find reports of the anti-acid efficacy of oral lansoprazole in this defined group.

Premature VLBW infants are routinely admitted to the Neonatal Intensive Care Unit (NICU) in our hospital and are usually routinely fed by naso-gastric tube.

Gastric aspiration before the next nasogastric feed is part of the routine treatment protocol. Hence we had the opportunity of measuring the pH of the aspirated contents before each tube feed. This gastric aspirate would otherwise have been discarded.

Infants from this group, with a clinical diagnosis of GERD formed the treatment group and received lansoprazole by naso-gastric tube administration. Confirmatory oesophagoscopy was not used in this study and clinical suspicion alone triggered treatment.

The control group consisted of infants who were being tube fed for other reasons. The common reason for tube feeding was the presence of prematurity and VLBW.

MATERIALS AND METHODS

This study was an audit to discover if the current therapy for clinically diagnosed premature babies with VLBW actually reduced gastric acidity. We simply measured the acidity of gastric fluid which had been aspirated before the next feed as part of the treatment protocol of tube-feeding.

The matter of approval with the ethical committee was discussed by all the authors and it was not thought to be necessary.

Infants who were premature were routinely admitted to the Neonatal Intensive Care Unit soon after birth. Details of weight; age: sex ratio are given along with pH levels in Table I.

Two samples of fasting gastric juice were obtained in from each baby. One before and one after 7 days lansoprazole in the treated group . Similarly two specimens were obtained from the control babies One on entry and one after 7 days of tube feeds.

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The control group was younger [mean of 2 weeks of age compared to 3.6 weeks] but the mean weight was almost the same [1.27kgm compared with 1.13 kgm]. The parents of the infants were told about the study and were given a printed sheet explaining that the purpose of the study was to grade the presumed acid- lowering effect of lansoprazole. They were free to withdraw their consent. None did.

2 aspirates, one from each group, were not used since the volume was so low that a dilution of over 100 was necessary for analysis. Dilutions of 50 were accepted.

Treated group n=10
Mean weight 1.13 +/- 0.03 kgm Mean Age 3.6 +/- 1.49 weeks
Ten consecutive babies with suspected GERD were treated as per a standard protocol. A nasogastric tube was passed to allow tube feeding at 4 hourly intervals with milk formulae (expressed milk feeds). Four hours after the last feed (and just before the next feed) the stomach was aspirated dry and the aspirate was analyzed.

Lansoprazole syrup (1.5 mg/kg body weight) was given daily via the tube in two divided doses 12 hours apart. The medication was kept in the refrigerator at 4°C and taken out from the refrigerator half hour before it was given.

Control group n=9
Mean weight 1.27 +/- 0.28 kgm Mean Age 2 +/- 1.37 weeks
Nine matched infants who required tube-feeding for a variety of reasons formed the control group. Lansoprazole treatment was not given but the collection of fasting gastric juice was carried out in the same way.

A variety of medication was given to both controls and treated babies for particular reasons. It was not possible to compute these possible effects but no particular difference existed in the variety of medication between the groups.

The volume of each gastric sample was recorded. The gastric fluids were stored in the refrigerator at 4°C prior to acid determination. Unless stated otherwise, distilled water was used throughout the experiment. It was routine practice to give daily prophylactic ferric ammonium citrate (FAC) 0.5 mL by tube feed to all the premature babies at 4 weeks of life. Thus 6/10 treated infants and 7 /9 control infants were below 4 weeks on entering the study and hence did not receive FAC. 3 infants from the treated group entered the study at 3.5 weeks of age and hence would have started FAC therapy between the first and the second specimens. One of these infants (infant 9) was the only one who became more acid on the second specimen. The other 2 infant (infant 8 and infant 4) did not noticeably become more alkaline than the other treated infants . We believe that because of this, it is possible to discount an alkalinizing influence from the FAC.

Acid determination using titrimetry
The solution of 0.01M sodium hydroxide used for the titration was first standardized using 0.01M hydrochloric acid and phenolphthalein as indicator. The gastric samples were appropriately diluted to volume in a 10mL-volumetric flask. Typical dilutional factors of between 20-50 times were required in view of the small volumes.

Two specimens were so small in volume that dilutions of 100 times were required. Since in these two cases inaccuracies were likely to be multiplied, these infants were excluded form the study.

Then 4mL aliquots of the diluted gastric samples were titrated with the standardized 0.01M sodium hydroxide using phenolphthalein as indicator. The volume of 0.01M sodium hydroxide consumed in the titration was recorded when the indicator turned pink in colour. For each gastric sample, acid determination was carried out in duplicate to obtain an average pH value. The difference in pH values between the first and second samples was recorded.

RESULTS

The mean pH for the first specimen in treated group was 1.04 compared to 1.17 in the control group (Figure.1). No infant was being ventilated or being fed intravenously

Treated Group
The mean and standard deviation of the first specimen was compared to that of the second specimen. This data was subjected to statistical analysis using the Student's t distribution in SPSS (version 11.0).Significance of the effect was compared with LSD at 5% level.. This difference reached statistical significance ($p<0.05$) in the treated group only. [Figure 1].

There was similarly a highly significant difference ($p<0.02$) between the initial pH and pH after 7 days treatment using a 1 sample test and a paired sample test.

With the exception of Subject 9, an increase in pH (decrease in the acidity) of the fasting gastric juice was observed in each infant [Figure 2a].

Control Group
In the Control Group, the change in the pH was quite variable with no constant trend and no significant difference was noted. [Figure 2b]. The conditions which led to admission and tube feeding frequently involved respiratory distress syndrome , pulmonary hemorrhage, biventricular hemorrhage as well as prematurity. A variety of medication was also prescribed to both groups.

DISCUSSION

Our results show that the fasting pH of the second specimen is increased and that acidity is reduced only in the treated group.. One further important finding was to confirm very low fasting pH levels in both the treated and the control infants.

The pH levels recorded of less than 2 even after treatment suggest that this dose of PPI given did not protect infants of this age from acid-induced oesophagitis.

This phenomenon of neonatal hyperacidity has a ready explanation in the peak fasting hypergastrinaemia around 8 days of life which is not further increased by a feed [9,10,11,12.] Around 3-4 months of age , the fasting hypergastrinaemia

Table I: Comparison of gastric pH in case and control groups

Treated Group						Control Group					
Subject's particulars				pH		Subject's particulars				pH	
Subject No	Sex	Weight* (kg)	Age (Wks)	Before medication	After medication	Subject No	Sex	Weight* (kg)	Age (Wks)	At sampling	1 wk after sampling
1	Girl	1.395	6	1.07	1.17	1	Boy	1.045	4	1.16	1.43
2	Boy	1.210	5	0.75	1.06	2	Boy	1.595	1	1.51	0.87
3	Girl	1.170	5	1.40	1.88	3	Girl	1.560	1	0.69	1.41
4	Boy	1.080	3.5	1.29	1.38	4	Girl	1.400	2.5	1.09	1.28
5	Boy	0.930	2.5	0.91	1.27	5	Boy	1.140	4.5	1.35	1.56
6	Boy	0.760	4	1.11	1.19	6	Girl	0.835	1	1.28	1.04
7	Boy	1.430	2	0.66	1.11	7	Boy	1.140	2.5	1.04	1.89
8	Girl	0.885	3.5	1.02	1.59	8	Boy	1.090	1	1.28	1.09
9	Boy	1.200	3.5	1.20	1.19	9	Girl	1.645	2.5	1.12	0.98
10	Girl	1.240	1	1.03	1.28						

Details of subjects' age, sex and weight at birth in case and control group. * Mean weight values for babies in case and control groups are 1.130 kg and 1.272 kg respectively

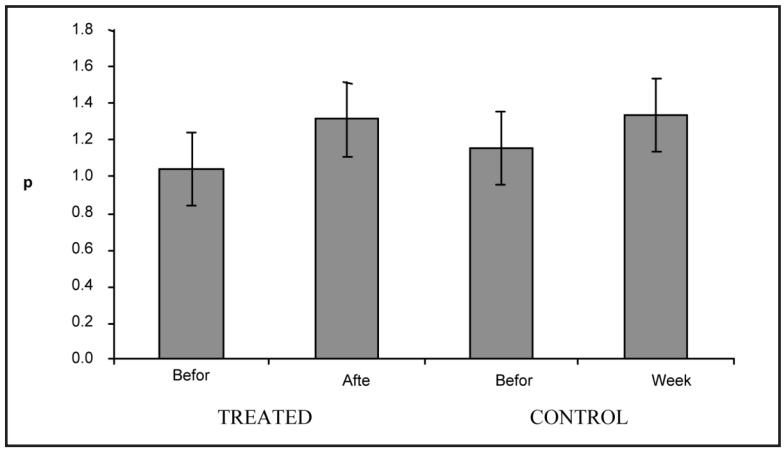

Fig. 1: Comparison of gastric pH in case (treated) and control groups.
Gastric fluids from 10 subjects in case group and 9 subjects in control group were analyzed for acid at one week interval. Significance at $p < 0.05$.

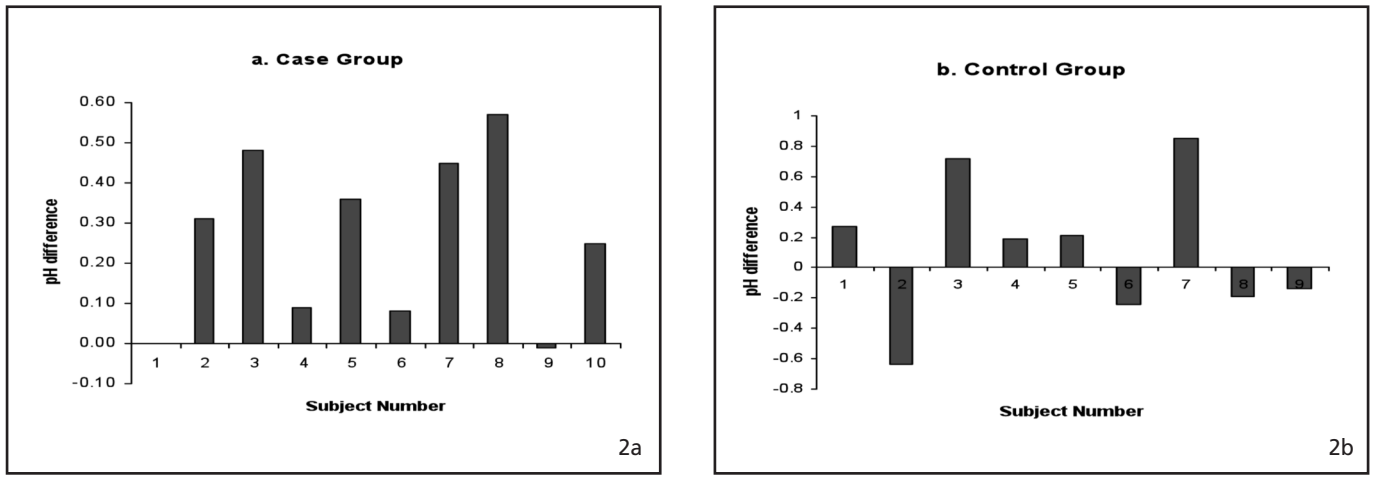

Fig. 2: pH difference in gastric fluids of case group (a) before and after lanzoprazole treatment and control group (b).
Gastric pH levels of subjects in the case group before and after treatment with lanzoprazole and control group were determined using titrimetry. Standard deviation values for case group and control group are 0.2095 and 0.5204 respectively

gradually reduces and a post-prandial response develops [11]. To explain these findings it has been proposed that this early autonomous gastrin is initially not reduced by gastric acidity and that the negative feed-back with gastric acidity only develops between 3-4 months[11,13].

When the negative feed-back matures, hyperacidity becomes under control because it is no longer being driven by an autonomous gastrin secretion [13]. The failure of exogenous histamine to evoke an acid response in preterm babies has been explained by Hyman as being due to acid already being maximally stimulated (by gastrin) at that time [8]. In a sense these babies from the age of 8 days to 3 months weeks of age with high acids and high gastrins may be considered as a temporary form of Zollinger Ellison syndrome simply caused by autonomous gastrin secretion. This hypothesis is further supported by acid secretory studies which reveal peak natural and peak histamine –stimulated acid secretion around 4 weeks of age [7,8].

The developing gastrin is known to have a trophic effect on the gastric mucosa with parietal cell hyperplasia as a result [12]. It is of interest to observe that this gastrin rise only occurs in the enterally fed baby [12].

Hence there are grounds to consider that PPI drugs, which are effective in older age groups, may have a reduced effect in the group which we studied. Either the acid and gastrin challenge may be too great or the dosage or efficacy of omeprazole may be too small.

The correct dosage of lansoprazole for appropriate acid –reduction and /or clinical relief, has not been determined in this age group. In a large survey of PPI utilization in infants, body weight dosage patterns for lansoprazole varied from 0.26-6.26 mgm/kgm/day (mean 1.83 mgm/kgm/day). Omeprazole dosage was approximately 60% of the lansoprazole dose. and the mean duration of treatment for both groups was 115 days. Clinical and/or acid-blocking effects were not recorded [3].

Our infants were treated with over twice the body weight dose of lansoprazole than the slightly older group treated with omeprazole (0.7mgm/kgm/day) by Omari and colleagues with a demonstrable acid-blocking effect [4]. Hence it is unlikely that inadequate dosage was the explanation for our failure to reach the accepted safe pH of 4 after 7 days treatment.

Indeed, recent data from 2 studies suggests that the metabolism of lansoprazole before 10 weeks of age is less efficient than after 10 weeks of age [14,15]. After similar body weight doses, the maximum concentration of lansoprazole in those younger than 10 weeks was 2- to 3-fold higher than in infants older than 10 weeks. In these studies for similar body weight doses the anti-acid effect was more pronounced in the infants below the age of 10 weeks.

The pH levels in our infants before treatment recorded 4 hours after the last feed, are similar to those reported in healthy preterm infants (mean weight 2614gm) (mean post-menstrual age 36 weeks) when assessed by gastric pH sensors The mean post-natal age is not given [6]. Higher fasting pH levels are generally reported in full term healthy babies at around 4 weeks of age [16].

The post- treatment pH, although less acid, continues to be sufficiently acid to pose a threat when reflux occurs.

The most accurate method of comparing acid secretory status between our treated and control infants would have been to have computed a 24 hour integrated gastric acidity. Unfortunately this technique was impractical in view of the low volumes of aspirate available. pH estimation was easy and practical and in this audit statistical differences were obtained.

We believe that had we been able to measure acid output in real terms (and not a logarithmic computation) the differences may have been more striking.

CONCLUSION

When measured after 7 days of treatment oral lansoprazole in the dose of 1.5 mgm/kgm /day given in 12 hourly doses reduces acid secretion in premature infants between 1 and 6 weeks of age. The degree of reduction in acidity is insufficient to protect pre-term VLBW infants from continuing episodes of acid reflux oesophagitis.

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This audit was independent and none of the authors had a competing interest.

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