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Esophageal impedance baselines in infants before and after placebo and proton pump inhibitor therapy

Short title

Impedance baselines after acid suppression

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Abbreviations

DIS	Dilated intracellular spaces
GER	Gastroesophageal reflux
GERD	Gastroesophageal reflux disease
I-GERQ-R	Infant Gastroesophageal reflux questionnaire
IQR	Inter quartile range
NERD	Non erosive reflux disease
PPI	Proton pump inhibitor
RCT	Randomized controlled trial
RI	Reflux Index
SAP	Symptom association probability

ABSTRACT

Background

Esophageal impedance monitoring records changes in conductivity. During esophageal rest impedance baseline values may represent mucosal integrity. The aim of this study was to assess the influence of acid suppression on impedance baselines in a placebo controlled setting.

Material and Methods

Impedance recordings from 40 infants (0-6months) enrolled in randomized placebo controlled trials of proton pump inhibitor (PPI) were retrospectively analyzed. Infants underwent 24hr pH-impedance monitoring prior to and after two weeks of double blind therapy with placebo or a PPI. Typical clinical signs of gastroesophageal reflux (GER) were recorded and I-GERQ-R questionnaire was completed.

Key results

Median (IQR) impedance baseline increased on PPI treatment (from 1217 (826-1514) to 1903 (1560-2194) Ohm, $p<0.001$) but not with placebo (from 1445 (1033-1791) to 1650 (1292-1983) Ohm, $p=0.13$). Baselines before treatment inversely correlate with the number of GER, acid GER, weakly acid GER, acid exposure and symptoms. The change in baseline on treatment inversely correlates with acid exposure and acid GER. Patients with initial low baselines have no improved symptomatic response to treatment.

Conclusions and Inferences

Impedance baselines are influenced by GER and increase significantly more with PPI therapy than with placebo. Clinical impact of this observation remains undefined as targeting therapy at infants with low baselines does not improve symptomatic response to treatment.

Keywords

Diagnostic testing

Esophagus

Esophageal motility

Paediatrics

pH-impedance monitoring

Proton pump inhibitors

INTRODUCTION

Esophageal multichannel intraluminal impedance is used for the detection of gastroesophageal reflux (GER) episodes in infants, children and adults (1-3). This is a technique to measure esophageal flow represented by changes in conductivity of adjacent contents between multiple electrode pairs on a catheter (4). Impedance values, representing changes in conductivity, drop in the presence of highly conductive contents, such as saliva or gastric fluids indicating a liquid swallow or GER. Less conductive boluses, such as air, cause an increase in impedance signal. When the esophagus is at rest, the impedance signal, referred to as the impedance baseline, is likely to reflect the conductivity of the esophageal mucosa (5-8). Low baselines have been observed in patients with esophagitis (6), NERD patients, patients with pathological acid exposure (7) and in patients with impaired esophageal motility (9). Farré et al have demonstrated that impedance is a useful tool for the evaluation of mucosal integrity and that patients with GER disease (GERD) and non-erosive reflux disease (NERD) have lower baselines compared to healthy volunteers (10). The authors report that the changes in baseline are not only related to macroscopic changes and secretion of inflammatory fluids, as seen in esophagitis, but to more subtle changes in the esophageal mucosa such as dilated intracellular spaces (DIS). DIS have been postulated to be the mechanism underlying NERD, providing a pathophysiological explanation for increased acid perception (11, 12). A significant correlation has been observed between the sensation of pain after acid infusion and baseline values suggesting a relationship linking baselines, DIS and perception of pain (10).

In infants and children proton pump inhibitors (PPIs) are the most commonly used therapeutic agents for the treatment of GERD. PPI therapy is proven effective for healing esophagitis in adults (13-15), for reducing acid exposure in infants (16-18) and is suggested to heal erosive esophagitis in 89% of children (19). However PPIs have not been proven to relieve symptoms of GERD in infants (20-22). The diagnosis and treatment of infantile GERD remains controversial with no evidence supporting empirical PPI therapy for treating GER clinical signs, such as irritability, vomiting and feed refusal (21, 23).

With endoscopy being difficult to perform in infants, impedance baselines may potentially be a marker of changes to mucosal integrity likely in increase symptom perception and therefore supportive of a diagnosis of GERD and a justification for PPI therapy. We have recently reported an increase in impedance baseline values in infants on PPI therapy in an open label, non placebo controlled trial (5). These data suggest that PPIs may change mucosal integrity through suppression of gastric acid and restoration of DIS. This effect was most prominent in those with initial low baselines. These findings are however uncontrolled, therefore we reanalyzed impedance recordings from infants with clinical signs of GERD, enrolled in randomized placebo controlled trials of PPI. We hypothesize that PPI treatment increases impedance baselines whereas placebo does not and that patients with lower baselines have more GER clinical signs and benefit more from therapy.

MATERIAL AND METHODS

Patients

Patient data from a research database compiled of data from previously conducted randomized controlled trials (RCT) of anti-reflux therapies were reanalyzed. RCT protocols

were approved by the Human Research Ethics and Drug Therapeutics Committee of the Women's and Children's Hospital, Adelaide, Australia.

Protocol

Preterm and term infants from zero to six months of age were enrolled. Infants were included if they presented with clinical signs suggestive of GER such as irritability, crying, excessive vomiting, regurgitation, coughing, feed refusal, unsettled behavior, back arching, failure to thrive or apneas and had failed to respond to non-pharmacological therapy. Patients underwent eight hour pH-impedance monitoring and clinical signs were continuously recorded by trained staff. Episodes of vomiting, regurgitation, irritability, crying, fussing, cough, sneeze, backarching, choking, gagging were scored during the study. Primary caretakers completed a validated infant questionnaire, the I-GERQ-R (24). After the eight hour hospital based study, the pH-impedance probe was left in place for 24 hr GER assessment either in hospital or at home.

GER and impedance baseline values were recorded using a single use infant pH-impedance catheter with seven sensors (six impedance channels) spaced 1.5 cm apart (ComforTec MII/pH probe, Sandhill Scientific, Highlands Ranch, CO, USA). The pH sensor was placed at the third vertebrae above the diaphragm as confirmed by a thoracic X-ray.

After the initial study patients were randomized (double blind) and received two weeks of PPI (omeprazole 1 mg kg^{-1} day^{-1} once daily; esomeprazole 0.5 mg kg^{-1} day^{-1} once daily) or placebo which consisted of bicarbonate solution (vehicle used in PPI preparations). For the purpose of this study the groups receiving omeprazole and esomeprazole are combined into one 'PPI group'. Eight hour pH-impedance, manual symptoms scoring, I-GERQ-R and 24hr pH-impedance monitoring was repeated on therapy after two weeks.

Data analysis

Impedance analysis

The eight hour and 24hr pH-impedance tracings (Bioview; Sandhill Scientific) were analyzed by two observers for the presence of liquid and mixed bolus GER. Distal esophageal acid exposure time, reflux index (RI) was calculated as the % time pH<4. I-GERQ-R scores were calculated as previously described (24).

Baseline calculation by automated analysis

Raw impedance values for all catheter channels were exported from each recording in text format at one sample per second. The baseline value per channel was estimated for both the initial 8h symptom assessment period and the full 24h study period using automated analysis procedures performed on the raw impedance data using a Matlab™ based algorithm. The algorithm was designed to filter the data, by removing the influence of rapid impedance dips and rises typically associated with reflux episodes and swallowing.

The algorithm operated as follows:

Firstly all data samples >5000 Ohm (representing gas reflux) were excluded. We assumed that the majority of liquid reflux related impedance drops to be excluded would have durations of <10sec. Each 10min period of tracing was therefore divided into separate 10sec intervals and the lowest level impedance was determined for each interval (Figure 1A). Of the sixty impedance values sampled, those above and below one standard deviation of the mean were removed (Figure 1B) and the mean of the residual samples was used to estimate of baseline impedance for each separate 10min period (Figure 1B). This estimation of baseline impedance

was then performed for all consecutive 10min periods of the tracing and then the median of all periods was used to estimate impedance baseline for the entire study (Figure 1C).

The values derived via this automated analysis method have been separately validated against a more time consuming manual analysis method. In this validation baseline estimates for ten studies showed an excellent agreement (ICC 0.988, $p<0.001$) (person communication R van der Pol, Academic Medical Centre, Amsterdam).

Symptom analysis

For clinical signs analysis we calculated the sum of all clinical signs recorded by trained staff continuously monitoring infants during the eight hour study. Vomiting, crying and coughing episodes were assessed separately as well, as these were consistently observed in all infants. GER symptom association probability (SAP) was calculated for all clinical signs together and for vomiting, crying and coughing separately. The SAP is based on the Fisher's exact test calculating the probability that GER and the clinical signs are unrelated. The SAP is calculated as (1 – p) x 100% and a SAP of >95% is referred to as a positive SAP (1).

Statistical analysis

We report on the influence of therapy on baselines based on the 24 hour pH-impedance recordings. The data on correlation between baselines, GER, acid exposure and clinical signs are based on the eight hour pH-impedance study as clinical signs were only continuously and reliably monitored during this period.

The baseline data were not normally distributed and are shown as medians (interquartile range). Comparisons were made using Wilcoxon's signed rank test and Spearman's correlation statistics. Spearman partial correlations were performed to assess the influence of different

variables. A Spearman's r of 0 - 0.3 was considered a weak correlation, 0.3 - 0.6 a moderate correlation, >0.6 a strong correlation. Statistical significance is defined as $p<0.05$.

RESULTS

Data were derived from 40 preterm and term infants, 18 (45%) male between the age of zero and six months, mean age was 7 weeks (IQR 3-12 weeks). Eleven infants received treatment with esomeprazole, 16 infants received omeprazole and 13 infants received placebo.

Bolus GER parameters such as total number of GER episodes, acid GER, weakly acid GER, reflux index (RI) and number of clinical signs scored during eight hour monitoring for the different treatment groups are presented in Table 1.

Impedance baseline values in the esophagus

Median (IQR) impedance baseline values measured in the initial study at the six impedance segments on the catheter ranged from 1383 (1070-1794) Ohm in the most distal channel to 1125 (912-1856) Ohm in the most proximal channel, the third most distal segment showed the highest impedance baseline 1956 (1474-2295) Ohm. Baseline values of the entire esophagus measured over 24hrs (1436 (1196-1627) Ohm) are comparable to the values measured in the eight hour study (1454 (1209-1776) Ohm). The most prominent changes in impedance baselines occurred in the most distal, most exposed, impedance segment. Throughout the manuscript we report the baseline values in the most distal impedance segment if not indicated otherwise.

Impact of treatment on impedance baseline

The median (IQR) 24hr impedance baseline increased significantly following PPI treatment (from 1217 (826-1514) to 1903 (1560-2194) Ohm after therapy, p<0.001) but not with placebo (from 1445 (1033-1791) to 1650 (1292-1983) Ohm after therapy, p=0.13). The change in baseline in the placebo and PPI group is shown in Figure 2. The change in baseline at different measuring points in the esophagus is presented in Table 2.

Impedance baselines in relation to other parameters

Before therapeutic intervention, impedance baselines are inversely correlated to the number of GER episodes, acid GER episodes, weakly acid GER episodes, reflux index, GER related clinical signs and vomiting episodes (Table 3). I-GERQ-R outcomes, number of cough episodes and number of crying episodes did not correlate to baseline values at any time.

The difference in impedance baseline during therapy showed an inverse correlation to the difference in reflux index and the number of acid GER episodes across all groups (Spearman r = -0.41 (moderate), p=0.009 and Spearman r = -0.38 (moderate), p=0.015 respectively). Subdividing groups based on treatment did not reveal other correlations.

Outcome for different initial baselines

Although we observed an inverse correlation between impedance baselines and the numbers of clinical signs, we did not observe a different response to treatment in patients with low baselines in terms of the total number of clinical signs recorded, crying, vomiting or coughing episodes. We used cut off values for low baselines of <1000, <1250, <1500, <1750 and <2000 Ohms. Including only patients with a positive GER – symptom association based on a positive SAP before treatment did not change these results.

DISCUSSION

In this study we assessed the influence of acid suppression therapies on impedance baseline values and the relation between impedance baseline and clinical signs in patients enrolled in RCTs performed in our centre. We demonstrate that PPI treatment significantly increases impedance baseline, whereas treatment with placebo does not. Lower impedance baselines pre treatment correlate with higher total number of GER episodes, number of acid GER episodes, number of weakly acid GER episodes, reflux index and number of GER related clinical signs. The increase in impedance baselines on therapy correlates with the reduction in acid exposure as well as number of acid GER. These findings suggest that impedance baseline values may reflect integrity of the esophageal mucosa which appears to be driven by the balance between damage caused by bolus GER, acid exposure(7) and possibly other factors (12, 25, 26) and protection by the tight squamous epithelium of the esophageal mucosa.

In our population we have established that impedance values throughout the esophagus are rather consistent, with the exception of the channel nearest to the heart and aortic arch. In that channel the narrowing of the esophagus most likely explains the rise in impedance baseline measured. Largest differences with therapy were seen in the most distal segment which is also the segment most exposed to gastric refluxate. This has also been observed by others (7, 10),

Although correlations do not prove causality, it is interesting that we observed an inverse correlation between impedance baselines and total numbers of GER, both weakly acidic and

acidic, acid exposure, and GER related clinical signs before treatment. It has been shown that acid and weakly acid solutions can cause DIS in adults (10, 12). Furthermore, DIS can present in adult patients with NERD (27-29). Moreover, increased DIS has been associated with increased perception of heartburn in NERD patients (12). It can be argued that infants are similar to adults with NERD in terms of GER like clinical signs without erosive esophagitis. Barlow has postulated a unifying hypothesis for the pathogenesis of heartburn in patients with NERD(11); the presence of low tissue resistance enables the diffusion of H+ ions into the intercellular space, activating chemosensitive nociceptors whose signals are transmitted to the brain and perceived as heartburn. This hypothesis could explain the correlation we observed between more acid GER and lower baselines and between lower baselines and increased number of clinical signs.

The role of weakly acidic GER has not been addressed in this hypothesis. It has been shown that infusions with weakly acid solutions cause similar DIS to acid solutions (12). This is not supported by our findings that patients on PPI treatment, who have more weakly acid GER have higher impedance baselines. The exact relation between weakly acid solutions, weakly acid GER, DIS and baseline levels remains to be established.

Anti reflux treatment in infants has been controversial, largely due to the fact that no treatment has been proven effective for reducing clinical signs of GER (21). Based on the observation that low baselines correlate to acid induced heartburn in adults we hypothesized that patients with low baselines before treatment would benefit more from treatment. However we did not observe a change in clinical signs on treatment in any of the groups, neither did we observe a correlation in change in baseline and change in clinical signs. Only a

few patients had low baselines and therefore this negative finding may be due to insufficient statistical power. It should be noted however that an increasing number of placebo controlled trials have failed to demonstrate symptomatic improvement with PPI. Hence the most likely conclusion is that the clinical signs suggestive of GER such as crying, irritability and coughing are very non-specific to GERD in infants.

A limitation of this study is that endoscopic data are unavailable to correlate the change in baseline to esophageal macroscopic mucosal findings and histology. This data is difficult to acquire because endoscopy is infrequently performed in infants and only performed in those who have severe complications and are therapy resistant. However, based on Farré et al's (REF) recent observations that clearly link impaired esophageal mucosal integrity to impedance baseline measurements (10), this study suggests that PPI's may improve mucosal integrity compared to placebo.

Although a relationship between symptom severity and baselines was not identified, these results are nevertheless of clinical relevance. Future research should assess if impedance is able to detect patients at risk for esophagitis. Impedance measurements are easier and safer to perform in infants than endoscopy and therefore has great potential in this patient population. Furthermore a better tool to identify patients who will respond to treatment is much awaited. Whilst symptomatic changes do not appear to correlate with changes in impedance baselines in the patient cohort studied, this approach may still have potential and is worthy of further investigation in older patients who may benefit by repeat investigations to evaluate mucosal healing (????).

In conclusion, we have demonstrated that PPI therapy increases esophageal baseline levels suggesting that PPI's improve esophageal mucosal integrity whereas placebo does not have this effect. Infants with low baselines before therapy do not have a better response to treatment in terms of numbers of clinical signs compared to infants with high initial baselines, the clinical relevance of esophageal impedance baselines requires further examination.

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Contribution

CL and RW performed the study. CL, RW and TO analyzed the data. CL wrote the manuscript. CL, MvW, MB, GD and TO designed the study and critically reviewed the final manuscript.

Disclosure

No conflict of interest to declare

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Table 1. GER parameters pre and post treatment

	Placebo N=13		
	Pre treatment	**On treatment**	**p-value**
GER total	76 (60-102)	70 (56-101)	0.81
GER acid	30 (12-48)	22 (11-28)	0.39
GER WA	45 (33-67)	55 (33-72)	0.44
Reflux index	31 (15-59)	26 (20-40)	0.6
Clinical signs	146 (135-201)	166 (131-209)	0.25

	Antacid N=13		
	Pre treatment	**On treatment**	**p-value**
GER total	49 (29-68)	31 (22-41)	0.023
GER acid	15 (4-26)	6 (2-22)	0.05
GER WA	27 (21-44)	20 (15-29)	0.093
Reflux index	1.2 (0.7-12.3)	4.6 (0.1-10.7)	0.05
Clinical signs	131 (83-208)	138 (105-220)	0.2

	Omeprazole N=16		
	Pre treatment	**On treatment**	**p-value**
GER total	46 (36-58)	30 (22-43)	<0.001
GER acid	17 (8-26)	2 (0-8)	0.001
GER WA	32 (23-46)	25 (18-37)	0.133
Reflux index	14.8 (3.7-23.1)	1.4 (0.1-4.3)	0.008
Clinical signs	105 (70-158)	119 (90-151)	0.88

	Esomeprazole N=11		
	Pre treatment	**On treatment**	**p-value**
GER total	131 (78-215)	89 (51-152)	0.041
GER acid	39 (17-91)	5 (2-11)	0.003
GER WA	87 (40-130)	78 (46-134)	0.213
Reflux index	46.9 (30.4-55.9)	10.2 (0.2-34.0)	0.006
Clinical signs	171 (145-191)	140 (123-186)	0.25

GER parameters per treatment group. Reflux index in % acid exposure during the study. Clinical signs are the total number of clinical signs recorded during the eight hour study.

Table 2. Baseline values per 24 hr study pre and post treatment

		Baseline Pre	Baseline Post	p-value
Placebo	N=13	1445 (1033-1791)	1650 (1292-1983)	0.13
Antacid	N=13	1619 (860-2215)	1546 (869-2408)	0.237
Omeprazole	N=16	1167 (856-1579)	1976 (1649-2067)	0.005
Esomeprazole	N=11	1291 (666-1493)	1903 (1254-2239)	0.006

Table 2 Baseline values per 24 hr study pre and post treatment for the most distal channel. Wilcoxon signed rank test.

Table 3 Correlation between GER parameters and impedance baselines

	Correlation	Spearman's r	p-value
GER total	strong	-0,61	<0.001
GER acid	strong	-0,66	<0.001
GER weakly acid	moderate	-0,38	0.005
Reflux index	strong	-0,63	<0.001
Symptom total	moderate	-0,38	0.005
GER related clinical signs	moderate	-0.48	<0.001
Vomiting	moderate	-0.53	<0.001

Table 3. Correlation between GER parameters and impedance baselines before therapeutic intervention based on the eight hour study**.**

Figures legends

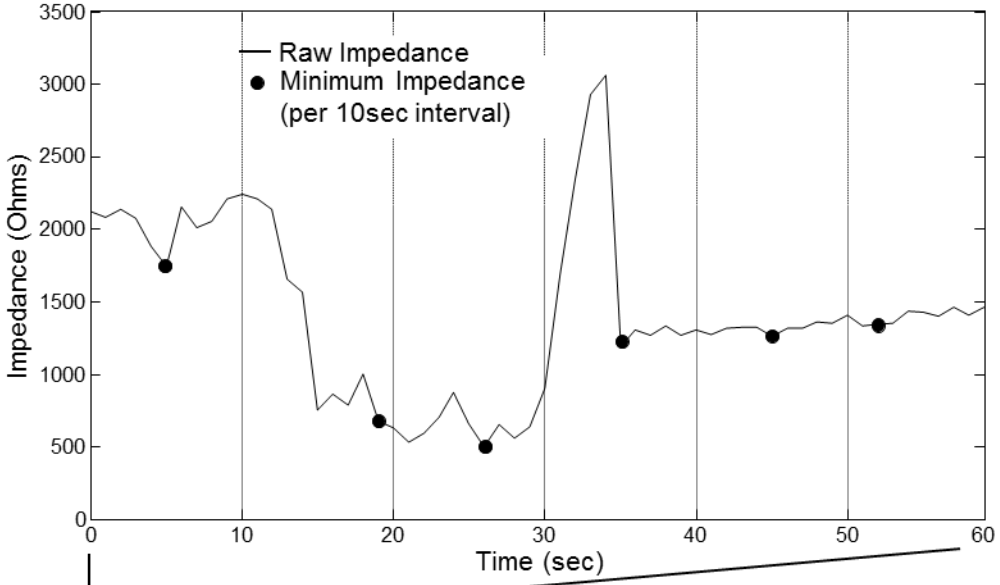
Figure 1. Automated calculation of impedance baseline values.

A. One minute time interval. The circles in the figure represent the 6 minimum impedance data points per minute used for the calculations.

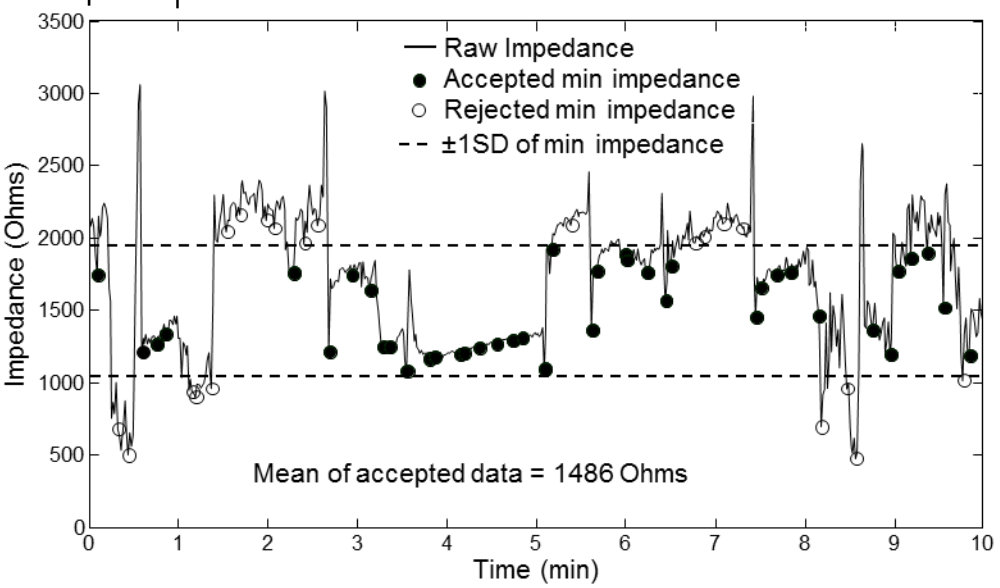
B. Ten minute time interval to calculated mean and standard deviation 60 samples (obtained from panel A). Samples above and below 1 standard deviation of the mean were removed (open circles). The mean of the remaining samples (closed circles) was calculated and this number was taken as the estimate of baseline impedance for each 10min interval.

C. Eight hour time interval. The analysis (panel B) was repeated for consecutive 10min intervals of the complete dataset and the median of all 10min intervals was used to estimate the overall impedance baseline value.

A.



B.



C.

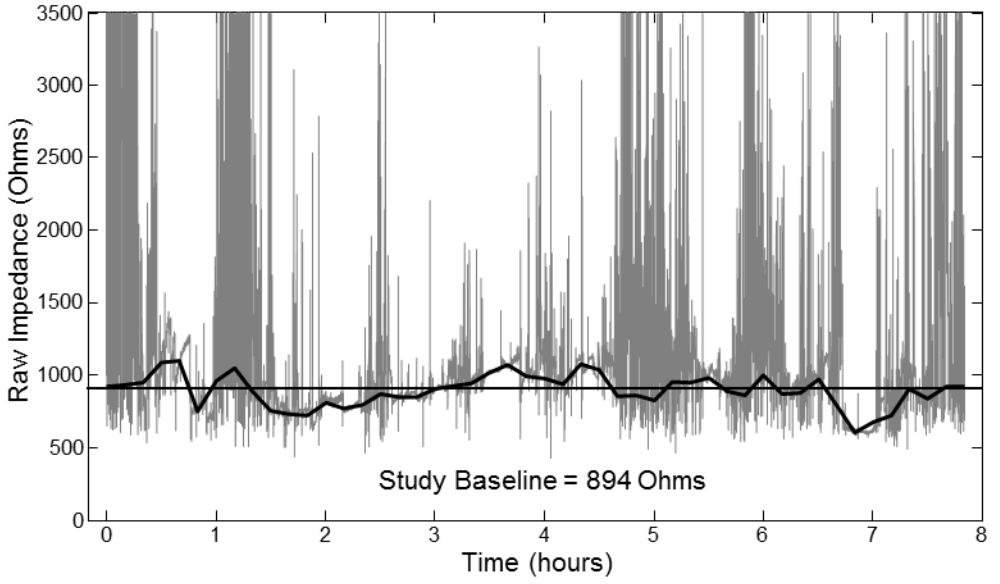


Figure 2. Difference in baseline post – pre treatment per treatment group

Difference in baseline value on treatment – pre treatment per treatment group. Baselines in the omeprazole and esomeprazole group are significantly increased compared to placebo. The difference between antacid and omeprazole and esomeprazole is p=0.055 and p=0.051 resp.