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Gastrokinetic Effect of Azithromycin: An in Vivo Sonographic Study on Healthy Volunteers

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Gastrokinetic Effect of Azithromycin: An in Vivo Sonographic Study on Healthy Volunteers

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Abstract

Background: Gastrointestinal hypomotility is a problem in many clinical conditions. There is a continuous search for new prokinetic agents. The macrolide, erythromycin has prokinetic efficacy but is less tolerated than azithromycin. Objective: To investigate the gastrokinetic effect of azithromycin. Method: Twenty four apparently health subjects were studied after an overnight fast. Thirty minutes before the study, placebo or azithromycin was orally administered in a crossover nature. Immediately before the study, subjects took a tin of milk (liquid) and 30 cl of ion free water. Serial sonographic measurements of gastric antral areas were obtained every five minute for thirty minutes. T-tests were conducted with $P<0.05$ used as a criteria for statistical significance.Result-Significant improvements in gastric emptying rates were recorded with azithromycin administration. Conclusion--- Azithromycin increases gastric motility and hence can be used as a possible gastrokinetic alternative to erythromycin. The assessment of gastric motility can be confidently done using a simple modality such as ultrasound

Keywords: Gastrokinesis, Sonography, Azithromycin

Introduction

Gastroparesis (GP) or gastric hypomotility is a chronic gastrointestinal motility disorder resulting from impaired transit of intraluminal gastric contents from the stomach into the duodenum associated with delayed gastric emptying in the absence of any mechanical outlet obstruction. Symptoms of GP are variable but include early satiety, nausea, vomiting, epigastric abdominal pain, and bloating. The prevalence of GP is very difficult to estimate due to the incomplete correlation of symptoms with gastric emptying, the large number of misdiagnosed patients who actually have this disorder, and the lack of widely available and standardized diagnostic tests or treatments. Although the true prevalence of thedisorder is unknown, an estimated one-third of diabetic patients in tertiary care settings have abnormal gastric emptying studies.[1]Furthermore, as much as 25–40% of adults and children initially diagnosed with dyspepsia are subsequently properly diagnosed with GP [2]. Accordingly ,this misdiagnosis can result in significant healthcare costs due to work days lost and prolonged hospitalizations [3, 4]. There is a continuous search for new gastrokinetic agents. Neostigmine has been used in the past for post operative paralytic ileus but it acts on many systems producing a lot of muscarinic adverse effects [5]. Metoclopramide is also used but it produces extra pyramidal effects while the use of cisapride is limited because of its cardiac toxicity[5] Erythromycin, a macrolide antibiotic has been used as a prokinetic agent for post operative ileus[6], gastric atony[7] and intolerance to

nasogastric feeding [8] in critically ill patients. It has been used to treat children with cyclic vomiting[9]. Some chronic conditions in which erythromycin has been tried are idiopathic constipation[10], chronic intestinal pseudoobstruction[11], diabetic gastroparesis[12] and functional dyspepsia[13]. Erythromycin is poorly tolerated because of its adverse gastrointestinal effect. Apart from erythromycin, many macrolide antibiotics are available, one of which is azithromycin. Compliance with therapy has been found to be better with azithromycin than with erythromycin [14].

Azithromycin is has been shown to inhibit the cytochrome isoenzymes as compared with other macrolides. Previous studies have shown that azithromycin increases antral motility, similar to erythromycin with longer duration of effect [15][16][17][18]. These studies lack randomized control data, making them methodologically weak and subject to bias. No data is available on the sonographic quantification of acute oral effect of single dose azithromycin. Many of the studies utilized manometry and scintigraphy which are not easily available and rather expensive. The aim of the present study was to observe the effect of azithromycin on gastrokinesis using a simple, inexpensive and non-invasive modality such as ultrasound.

Materials and Methods.

This study was a single centre, randomised, single-dose, placebo controlled two way crossover study in apparently healthy adult male volunteers. A pilot study on seven apparently healthy subjects showed that 30 cl of water taken alongside a tin of peak milk emptied from the stomach in about 25 to 30minuties.

The study was conducted in Anambra State, Nigeria. In line with Helsinki Declaration, approval for the study was obtained from the Human Research Ethics Committees of Nnamdi Azikiwe University and ST Charles Borromeo Hospital, Onitsha, Anambra State. The procedures were explained to the subjects (volunteers) and each subject signed a consent form before enrolling into the study. All subjects were aware of their option to withdraw from the study anytime they desired.

This study involved 24 apparently healthy male volunteers who received financial compensation for their participation in the study. This number was considered to have sufficient power based on prior experiences in studies with a similar design.[11] Potential subjects under went medical history, fasting blood sugar tests, occult blood tests and physical examination. Exclusion criteria included history of gastrointestinal diseases, metabolic disease (eg diabetes), peptic ulcer, and irritable bowel syndrome and the presence of gastroesophageal reflux. The subjects had no abdominal surgery except for appendectomy. They were instructed not to take drugs affecting gastrointestinal motility at least 10 days before examination [12]. Subjects with abnormal defecation such as constipation or diarrhea were excluded from the study. Smoking and snuff taking were prohibited for eight hours before and during the test[20]. The fasting blood sugar tests were conducted using portable blood glucose meter (Companion 2 Metre, Medisense, Waltham, MA) on the first day. Subjects were advised not to drink water or any other thing after 7.30am on each day of examination or at least one hour before the procedure.

The subjects were randomised into two groups (group A and B), with twelve subjects in each group. Group A started with placebo while group B started with azithromyicn in a cross over manner. At least, a ten day gap was given between azithromycin and placebo ingestion for each subject (12 subjects) in group B. 500 mg of azithromycin (Swiss pharma LTD) were supplied. In a similar study [22], Subjects received erythromycin 600mg per oral or placebo 30 minutes before the ingestion of a standard 200 ml liquid test meal.

Thirty minutes before the procedure, the subjects took azithromycin (500mg) or placebo with 20ml of water. Immediately before the placebo, the basal gastric antral measurement were obtained (antero-postenor and longitudinal dimensiosns) as a scout scan. Subsequently, the subjects ingest a tin of full cream peak brand milk (157ml, 170g, contents: vitamins and iodine, milk fat 9%, milk solids not fat 22%,

milk stabilizer E339, brand of Friesland Foods, WAMCO Nig Plc) immediately before the procedure. This was immediately followed by the drinking of 30cl of ion free [15]. Water (Eva water, Coca kola co, Plc). This gave 457 ml of liquid (milk and water). One minute was allowed for both milk and water intake as longer period would give rise to little residual fluid in the stomach. Both milk and water were stored in a large flask at room temperature.

The subjects were examined in supine position with a 3.5MHZ curve linear array transducer (Siemens sonoline SL-2, Issaquah, USA). Gastric emptying were monitored indirectly by determining the longitudinal and anteropsterior diameter of a single section of the gastric antrum using the abdominal aorta and the left lobe of the liver as internal landmarks to obtain the same standardized scanning level consistently accordingly as previously stated in literature [24]. This is shown in Figure 1 below. At each observation, the longitudinal (D_1) and anteropostenor (D_2) diameters were used to calculate the gastric antral area (GAA). The measurements of the gastric antrum were taken from the outer profile of the wall and obtained between antral contractions to provide a measure of the relaxed width of the antrum.[16] At this level the scan showed the stomach shape as either a circle or an ellipse, so the GAA was calculated thus

$$GAA=\frac{\prod xD_1 \times D_2}{} \quad \ldots \text{ Darwiche } \textit{et al}, 2004$$

The subjects were studied with minimal abdominal compression. Between examinations, the subjects were raised seated in a chair. Measurements were taken immediately before the test meal, 5, 10, 15, 20, 25, and 30 minutes after injestion of the test meal. This decision for 30 minutes timing was based on the result of the pilot study which showed that the test meal emptied completely from the stomach in about 25-30 minutes.

The methods for this procedure have been previously described and have been validated in health controls, correlating well with scintigraphic measurements [24]. At the end of the first stage of the procedure (placebo or azithromycin phase), the subjects' heights weights and ages were obtained.

The data obtained were analyzed using SPSS version 16.0 (SPSS INC., Chicago, Illionosi, USA). Gaussian responses of GAAs were tested using kolmogorov-Smirnoff test. Both descriptive and inferential statistics were conducted. Paired (repeated measure) t tests were used to test the differences in mean values of GAAs at placebo and azithromycin stages. $P<0.05$ was used as a criterion of statistical significance.

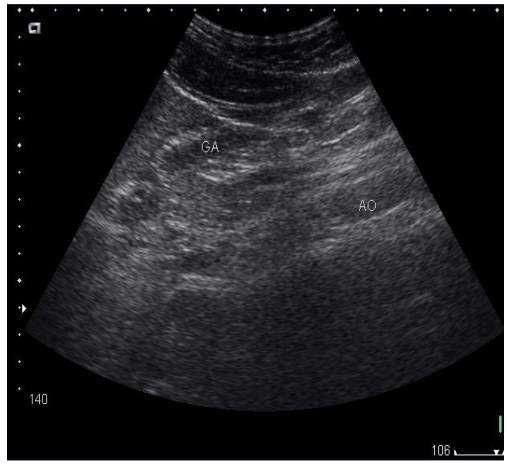

Fig-1 Sonographic vertical showing the gastric antrum, aorta and the liver.

Results

Twenty four male subjects entered and completed the study. Their ages ranged from 27 years to 40 years with a mean age ± standard deviation of 33.75 ± 4. 12years. The weight and height were recorded as 55kg-69kg and 1.62m-1.76m respectively. The mean ± standard deviations of weight and height were 65 ± 5. 96kg and 1.68 ± 0.06m respectively. GAA, gastric area in mm^3, Tx, time at which GAA was obtained in minutes.

Discussion

The macrolide antibiotic, erythromycin has long been used as a prokinetic agent. A pitfall in its usage is the development of antibiotic resistance which could be faster in erythromycin compared to other macrolides. In addition, erythromycin is less tolerated than azithromycin and as it is taken 3 or 4 times in a day, thus resulting in poor compliance.

Table-1 Stimulation of gastric emptying after administration of azithromycin.

	T_5	T_{10}	T_{15}	T_{20}	T_{25}	T_{30}
Mean GAA (Placebo+fatty meal)	1071.82	660.96	590.75	599.67	522.36	388.15
Mean GAA(Azithromycin-+fatty meal	668.6	569.21	357.07	384.41	353.83	428.15
P	0.002	0.29	0.00	0.00	0.00	0.49

The result of this study showed that azithromycin significantly increased gastric emptying in the first five minutes (table 1).This was deduced from the significantly lower GAA in the fifth minute in the azithromycin phase compared with the placebo. Their was a relative lag period in the 10^{th} minute as shown by the equality of mean values of the GAA in the 10^{th} minute for placebo and azithromycin phases. The increase in emptying rate as facilitated by azithromycin was sustained in the 15^{th} to the 25^{th} minute as shown by the significantly lower GAA with azithromycin at these periods .

The result of thus study is similar to that of a previous study on rabbit duodenum [5] which showed that azithromycin produced a significant prokinetic effect. A similar study on humans suggested that it could be used as an alternative prokinetic for the treatment of GIT dysmotility and perhaps gastroparesis. In the above study, it was noted that a higher dose of AZI created a statistically significant improvement in the motility index and higher mean amplitudes antral contractions in the postprandial period[1]. This report is congruent to previous studies [25][26] which showed that the macrolide, erythromycin has a gastrokinetic effect. From tolerance point of view, it could be accepted that azithromycin is a better gastrokinetic agent than erythromycin. Studies on the comparative effect of both macrolides are advocated in order to assess their relative clinical efficacy.

This cross over nature favoured the use of paired (repeated measure) t-test which is more powerful than the unpaired t-test as it removes the effects of confounding variables. It is therefore recommended that future studies in this area, comparing the gastrokinetic effects of two drugs should adopt cross over designs. A non commercially available analogue of erythromycin has previously been produced and reported in literature[27]. As macrolide bacterial resistance is a key disadvantage in the gastrokinetic use of erythromycin below therapeutic doses[28], It is therefore suggested that analogues of azithromycin, without antibiotic properties be commercially produced as gastrokinetic drugs.

This study has demonstrated the gastrokinetic efficacy of azithromycin in humans. Azithromycin hence can be used as a gastrokinetic alternative to erythromycin due to its greater tolerance among human subjects.

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