COMPARATIVE STUDY OF THE GASTROKINETIC EFFECTS OF ERYTHROMYCIN AND AZITHROMYCIN IN HEALTHY SUBJECTS: SONOGRAPHIC STUDY.

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ABSTRACT

AIM: The purpose of this study was to investigate the comparative gastrokinetic effects of erythromycin and azithromycin in apparently healthy subjects. METHODOLOGY: Ultrasonographic evaluation of changes in gastric antral areas were undertaken in 24 subjects after a liquid meal at five minutes interval for thirty minutes. These were performed in pre-prandial states in a cross over method between erythromycin and azithromycin ingestion. The gastric antral areas were calculated as compared used paired t test as a measure of relative motilities induced by these drugs. P<0.05 was used as a criterion of statistical significance. RESULT: This showed that azithromycin enhance gastric motility better than erythromycin. No significant difference after the 15th minute might imply that emptying of this liquid meal was concluded in the first 15 or 20 minutes.

CONCLUSION: Azithromycin hence could be adopted as a prokinetic alternative to erythromycin based on its tolerance and added efficacy in gastric motility.

KEYWORDS: Erythromycin, Azithromycin, gastrokinesis, ultrasonography.
INTRODUCTIO

Delayed gastric emptying,[1] antral hypomotility,[2] and impaired gastric accommodation[3] have been reported in patients with functional dyspepsia. Cross sectional studies have shown that gastric emptying is delayed in as many as 50% of diabetic patients, causing symptoms such as postprandial early safety, abdominal fullness, nausea, vomiting, and early postprandial hypoglycemia.[4] Gastric emptying is recognized as a major determinant of postprandial glycemia in both healthy[5] and patients with types 2 diabetes.[6] Interventions that reduce postprandial hyperglycemia, but modulating the rate of gastric emptying, have the potential to become mainstream therapies in the treatment of diabetes. Nevertheless, observations in both animal models and diabetic patients have, in general, been consistent with those obtained in healthy humans.[6]

Prokinetic agents, such as neostigmine, metoclopramide, cisapride are commonly used for treatment of such conditions but no agent has yet proved to be ideal so, there is always a search for new agents. Neostigmine produces, a lot of muscarinic adverse effects, metoclopramide produces extra pyramidal effects while the use of cisapride is limited because of its cardiac toxicity.[7]

The Macroclide antibiotic, erythromycin has been known to be associated with increased gastrointestinal motility since its introduction more than 45 years ago.[8] It acts on gut motility as an agonist of the receptors for motility and possibly via a cholinergic pathway or endogenous motilin release.[9] Some studies have shown that its administration at smaller doses than those used for antibiotic properties enhances gastric emptying of meals in healthy volunteers, as well as in critically ill patients and those with gastroparesis related to several pathologies, including diabetes.[10] Erythromycin has been found to be useful as a prokinetic agent in children with chronic constipation and presenting mega rectum and fecal impaction.[11]

Erythromycin is poorly tolerated because of its adverse gastrointestinal effects.[11] Compliance with therapy has been found to be better with azithromycin than with erythromycin.[12] The prokinetic effect of this second macrolide (azithromycin) has been established in a recent study,[7] but no study, to the best of knowledge has compared the gastrokinetic effects of these two macrolides. This study was designed to compare the gastrokinetic effect of acute oral administrations of erythromycin and azithromycin.
MATERIALS AND METHOD

STUDY DESIGN
This was a randomized, single blind, placebo-controlled two way crossover study in apparently healthy adult male volunteers of Ibo origin.

ETHICAL CONSIDERATION
Approval for this study was obtained from the Human Research Ethics Committee of Nnamdi Azikiwe University, Nnewi Campus, Anambra State, Nigeria. The procedure were explained to the participants(subjects) and each subjects signed a consent form before enrolling into the study. All subjects were aware of their option to withdraw from the study anytime they desired.

SAMPLE SIZE/SAMPLING
This study involved 24 apparently healthy male volunteers who received financial compensation for their participation in the study. This number of subjects was considered to have sufficient power based on prior- experience in studies with a similar design.[13,14]

Subjects selection
Twenty four apparently healthy male subjects were recruited for this study as it was easier to recruit males than females. Darwiche et al[15] reported a non significant difference in gastric emptying rates of males and females. Potential study subjects underwent medical history, fasting blood sugar tests, occult blood tests and physical examinations. Exclusion criteria included history of hepatobiliary diseases, gastro intestinal diseases or metabolic disease (eg diabetes), the presence or history of gastro-oesophageal reflux, peptic ulcer disease and irritable bowel syndrome. The subjects had no previous abdominal surgery (except for appendectomy). The subjects were instructed not to take drugs affecting gastrointestinal motility[16] at least 10 days before each day of examination. Patients 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 study.[15]

The fasting blood sugar was conducted using a 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 the of examination or at least one hour before the procedure.
DRUGS
Erythromycin (Medopharm, India) and azithromycin (Swiss pharma PVT, LTD) were supplied in 500mg. Single doses of drugs were administered. During the inter digestive state in humans, erythromycin 40mg induces a premature activity front that start in the stomach, while erythromycin 200mg induces a prolonged period of enhanced antral contractile activity.\(^{[17]}\) In a similar study by potincassa et al\(^{[18]}\) subjects received erythromycin(600 mg per oral) 30 minutes before the ingestion of a standard 200ml liquid test meal.

TEST MEAL
Immediately before the procedure, each subjects took 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 drinking of 30cl of ion free water (Eva water, coca cola Co, PLC).\(^{[19]}\) This gave 457 ml of liquid. One minute was allowed for both milk and water intake as longer period might give rise and water intake as longer period might give rise to little residual fluid in the stomach, both water and milk were stored in a large flask at room temperature.

PROCEDURE
Through computer generation of random numbers, the subjects were divided into groups A and B. group A (12 in number) started with erythromycin and crossed over to azithromycin after a wash out period of at least 10 days. Group B (12 subjects) started with azithromycin and crossed over to erythromycin (group A) after a wash out period of at least 10 days. This ‘wash out’ period is similar to that observed in a similar study.\(^{[20]}\) The participants were scanned on two separate visits to compare the effect of erythromycin and azithromycin on gastric motility using cross sectional area of the antrum at different time intervals. On arrival to the centre, the basal gastric antral area was measured as a guide to its location. Subsequently, erythromycin or azithromycin was taken with 20ml of water, 30 minutes before the procedure.

This 30 minutes timing and 500mg dosage have been applied in a similar study.\(^{[21]}\) Subjects were scanned between 0700 hours and 0900 hours.

The subjects were examined with a 3.5 MHZ curvilinear transducer(siemens sonoline SL-2, Issaquah, USA). Immediately before the procedure, the subjects ingested the milk and water
Gastric emptying were monitored indirectly by determining the longitudinal and anteroposterior diameters 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 (fig 1). \[^{22}\] At each observation the longitudinal (D1) and anteroposterior (D2) diameters were used to calculate the antral area. 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. \[^{22}\] At this level, the scan showed the stomach shape as either a circle or an ellipse, so the gastric antral cross-sectional area (GAA) was calculated by the following formula:

\[
\text{GAA} = \pi \times \frac{D_1 \times D_2}{4}
\]

The subjects were studied in supine position with the ultrasound transducer applied with the 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 ingestion of a test meal. The decision for the 30 minutes timing was based on the result of a pilot study which showed that this test meal emptied completely from the stomach in 25 to 30 minutes in controls. The subjects lay on the couch for transabdominal sonography. The methods for this procedure have been validated in healthy controls, correlating well with scintigraphic measurements. \[^{15, 22}\]

At the end of the procedure, subjects heights were measured on a calibrated vertical wall and weight measured on a weighing scale (Model H 89LT Blue). The ages of subjects were also obtained. All acquisitions were performed by one scientist to limit variability in statistical analysis.

Descriptive and inferential statistical analyses were conducted using SPSS software version 16.0 (SPSS INC.) Chicago, Illinois, USA. Gaussian responses of GAA at each time which served as indicator of motility were tested using Kolmogorov-Smirnoff test. Paired (repeated measures) t-test was used to test for the differences in GAAs at each time interval during erythromycin and azithromycin administration. Significantly lower GAA indicated greater motility. P<0.05 was used in the criterion of statistical significance.
RESULTS
Twenty four male subjects (age range: 27-40 years) entered and completed the study. Their mean age ± standard deviation was 33.75 ± 4.12 years.

Their weight (55-69 kg) and heights (1.62-1.76m) were recorded as 65 ±5.96kg and 1.68 ± 0.06m respectively.

Table 1 shows a comparative study between gastric antral areas at different periods during erythromycin and azithromycin ingestion with lower GAs at the 10th and the 15th minute post prandials. This showed that azithromycin enhance gastric motility better than erythromycin. No significant difference after the 15th minute might imply that emptying of this liquid meal was concluded in the first 15 or 20 minutes thereby giving no difference in GAA after these periods.

Table 4: Comparative Stimulation of gastric emptying after administration of erythromycin and Azithromycin

<table>
<thead>
<tr>
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<th>T_5</th>
<th>T_10</th>
<th>T_15</th>
<th>T_20</th>
<th>T_25</th>
<th>T_30</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean GAA(Erythromycin + fatty meal)</td>
<td>778.05</td>
<td>806.07</td>
<td>511.03</td>
<td>481.71</td>
<td>386.54</td>
<td>399.41</td>
</tr>
<tr>
<td>Mean GAA(Azithromycin +fatty meal)</td>
<td>668.66</td>
<td>569.21</td>
<td>357.07</td>
<td>384.41</td>
<td>353.83</td>
<td>428.15</td>
</tr>
<tr>
<td>P</td>
<td>0.053</td>
<td>0.013</td>
<td>0.006</td>
<td>0.075</td>
<td>0.261</td>
<td>0.67</td>
</tr>
</tbody>
</table>

GAA, gastric area in mm^3, Tx, time at which GAA was obtained in minutes

DISCUSSION
Macrolides have been found to have pharmacodynamic properties beyond their antimicrobial mode of action,[23] some of these include anti-inflammatory and immunomodulatory effects.
In these clinical situations, it is noteworthy that the macrolides are being used, often primarily, for their antibiotic effects on the diseases and the aforementioned ‘extra-antibiotic’ effects are an addition to this.

More recently, another extra-antibiotic effect of macrolides has been exploited; their function as a gastrointestinal prokinetic.\textsuperscript{[24]} Prokinetic agents are drugs that increase contractile force and accelerate intraluminal transit.\textsuperscript{[25]} Many studies have been carried out in a wide variety of patient populations and disorders, including gastro esophageal reflux in children,\textsuperscript{[26]} diabetic gastroparesis\textsuperscript{[27]} and functional dyspepsia.\textsuperscript{[28]} This has been investigated in erythromycin severally and to a lesser extent in other macrides.

Table 4 shows a faster emptying rate (gastric motility) induced by azithromycin over erythromycin in the 10\textsuperscript{th} and 15\textsuperscript{th} minute. There was no point at which erythromycin showed a higher impact on gastric motility than azithromycin. This indicates a gastrokinetic superiority of azithromycin over erythromycin. A previous study\textsuperscript{[7]} on rabbit duodenum also indicated a prokinetic effect of azithromycin.

Hence, from both the efficacy and tolerance point of view, azithromycin would be a preferred gastrokinetic agent to erythromycin.

The gastric antral areas over times were compared at different phases. This choice of paired t-test was favoured due to the crossover nature of the study, which removed the effects of confounding variables.

A non commercially available analogue of erythromycin has previously been produced and reported in literature.\textsuperscript{[29]} As macrolide bacterial resistance is a key disadvantage in the gastrokinetic use of macrolides below therapeutic doses, it is therefore commended that analogues of azithromycin, without antibiotic properties be commercially produced as gastrokinetic agents. This study has shown a gastrokinetic advantage of azithromycin and would have vast clinical applications in gastrokinesis.

\textbf{Conflict of interest}
None declared.
REFERENCES


