academicJournals

Vol. 7(33), pp. 2348-2351, 8 September, 2013
DOI 10.5897/AJPP2013.3476
ISSN 1996-0816 © 2013 Academic Journals
http://www.academicjournals.org/AJPP

African Journal of Pharmacy and Pharmacology

Full Length Research Paper

Comparison of the effect of azithromycin versus erythromycin on gallbladder motility: A sonographic study

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Accepted 4 June, 2013

Erythromycin is a known prokinetic (cholecystokinetic) drug. Recently, erythromycin has been linked to the occurrence of arrhythmias and cardiac death due to QT prolongation. Azithromycin is similar to erythromycin in structure, but has the least arrythmogenic tendency among all the macrolides. This study was aimed at determining the comparative cholecystokinetic effects of erythromycin and azithromycin. Twenty four apparently healthy males were studied in pre-prandial and postprandial states. Thirty minutes before the study (after an overnight fast), the subjects took 500 mg azithromycin and erythromycin in a randomized cross over method. Immediately before the ingestion of a standardized liquid meal, the length, width and height of the gallbladder was measured in each subject to obtain the ellipsoid volume using real time sonography and in supine position. After the ingestion of the liquid meal, the gallbladder measurements were obtained every 5 min for 40 min. The gallbladder contraction index (GBCI) was calculated for each period as a percentage change in volume using the fasting volume as the initial volume in all the calculations. The weight, height and age of each subject were obtained. Statistical analysis was conducted using Statistical Package for Social Sciences (SPSS) software; paired *t*-tests were used to compare GBCI values in erythromycin and azithromycin interventions. P<0.05 was the criterion for statistical significance. In majority of the periods, erythromycin showed significantly higher GBCI values than azithromycin; azithromycin showed higher GBCI values in few points. Erythromycin has cholecystokinetic superiority over azithromycin. From tolerance point of view, azithromycin should be the preferred drug as it does not have significant drug-drug interaction and may be a potential new treatment of cholestasis.

Key words: Sonography, erythromycin, azithromycin, gallbladder motility, cholecystokinesis.

INTRODUCTION

Gallbladder motility can be affected by various clinical conditions such as obesity, diabetes mellitus and celiac disease. In obesity, a condition characterized by increased risk of gallstone(s) as a result of decreased gallbladder motility has been reported (Fraquelli et al., 2003). Furthermore, decreased gallbladder motility are

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contributed by other factors including autonomic neuropathy, which reduces gallbladder sensitivity to cholecystokinin (CCK) or reduced the numbers of CCK receptors on gallbladder wall. CCK is not easily accessible in the therapy for gallbladder stasis, so this is an alternative. Progesterone (P) has an inhibitory effect on the contractility of gastrointestinal smooth muscle, including the gallbladder. Since P levels are elevated during pregnancy, biliary stasis may develop during pregnancy. This is characterized by an increase in fasting and residual volumes, and also by a decrease in emptying capacity (Kline et al., 2005).

Impaired gallbladder motility and delayed intestinal transit contribute to cholesterol and gallstone formation by impeding the enterohepatic circulation of bile salts and causing gallbladder stasis (Xu et al., 1998). The therapeutic value of erythromycin, a prokinetic motilin analogue, was evaluated in an animal model for gallstone formation. Erythromycin treatment for animals on high cholesterol diet, restored gallbladder contractility and intestinal transit to control levels, increased bile salt secretion, reduced the total bile salt pool, lowered the cholesterol saturation of bile, lengthened the nucleation time, and also reduced crystal formation. Erythromycin enhances gallbladder motility and hastens intestinal transit thereby promoting rapid enterohepatic cycling of bile salts. This increased bile secretion improves cholesterol solubility and reduces crystal development (Xu et al., 1998). Furthermore, erythromycin has been shown to be better than other commonly used prokinetic agents like domperidone, metoclopramide and cisapride as tachyphylaxis, and other adverse effects are obstacles to their use (Frazee et al., 1994).

Several reports of arrhythmias associated with use of either oral or intravenous (IV) erythromycin have been reported (Ray et al., 2004; Wisialowski et al., 2006; Milbery et al., 2002). In 2004, a large cohort study of Tennessee Medicaid patients from 1988 to 1993 showed a possible association between erythromycin with a risk of cardiac death through its extensive metabolism by the cytochrome P-450 3A isoenzymes (Ray et al., 2004). In his study, the adjusted rate of sudden death from cardiac causes was five times higher in patients on erythromycin than in patients on other antibiotics such as amoxicillin.

A previous study on the comparative prokinetic effect of erythromycin and azithromycin was centred on gastric motility (Moshiree et al., 2010). There has not been any sonographic study to the best of our knowledge, on the comparative cholecystokinetic effect of erythromycin and azithromycin using randomized controlled data. As a result, to the aim of this work was to study the comparative effect of erythromycin and azithromycin on gallbladder motility in apparently healthy subjects.

MATERIALS AND METHODS

This study was a single-centre, randomized, single-dose two way cross-over study in apparently healthy adult male volunteers. This study was placebo-controlled so as to avoid confounding variables like subject differences e.g. weight which will affect the validity of the research. The study was conducted in Leeds Hospital, Anambra State, Nigeria. In line with Helsinki Declaration, approval for this study was obtained from the Human Research Ethics committee of the Nnamdi Azikiwe University, Nnewi Campus, Anambra State. The procedures were explained to the subjects (volunteers) and each subject signed 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. This number was considered to have sufficient power based on prior experiences in studies with a similar design (Schauch et al., 1988; Mannaerts et al., 1998). Potential study subjects underwent medical history, fasting blood sugar tests, and physical examinations. Exclusion criteria included history of hepatobiliary diseases, gastrointestinal or metabolic disease (e.g. diabetes). Subjects who had chronic diseases (diabetes, sprue, achalasia, irritable bowel syndrome, truncal vagotomy, pancreatic insufficiency, sickle cell hemoglobinopathy, and hemolytic anaemia) or were receiving medications (e.g. morphine and morphine-related medications, atropine, calcium blockers, octreotide, progesterone, histamine 2 receptor stimulators, theophylline, glucagons and indomethacin) known to alter gallbladder contraction were excluded (Ziessman et al., 2001). The subjects were instructed not to take drugs affecting gallbladder (gastrointestinal) motility at least 10 days before the examination similar to a previous report in literature (Burkes, 2000). The fasting blood sugar estimation 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 6.30 am on the day of the examination and to report for each investigation after an overnight fast.

Erythromycin and azithromycin were supplied as tablets. Erythromycin (Medopharm, India) and azithromycin (SWISS Pharma PVT Ltd) were supplied in 500 mg. Immediately before the procedure, each subject took a tin of full cream peak brand milk (157 ml, 170 g, contents: vitamins and iodine, milk fat 9%, milk solids not fat 22%, milk stabilizer E339, brand of friesland foods, WAMCO Nig. Plc) followed by drinking of 30 cl of ion free water (Eva water, Coca Cola Co. Plc) (Arient et al., 1994). This amounted to 457 ml of liquid (milk and water) meal. One minute was allowed for both milk and water intake. Both milk and water were stored in a large flask at room temperature. The decision to adopt milk dilution was made by volunteers who indicated that they may have some sense of nausea if they take raw and undiluted milk.

Through a computer generated random numbers, the subjects were divided into two groups with 12 subjects in each group. Group A started with azithromycin and subsequently crosses over to group B, while group B started with erythromycin and subsequently after the “wash out” period crosses over to group A. At least a 10 day “wash out” period between the two interventions was adopted. The volunteers were scanned on two separate visits to compare the effects of erythromycin and azithromycin on gallbladder motility (contraction index). Subjects were examined between 0800 and 0900 after an overnight fast. Thirty minutes before the procedure (ingestion of test meal of milk and water), the subjects took the drug (500 mg erythromycin or 500 mg azithromycin) with 20 ml of water. This 30 min gap and 500 mg dosage have been used in a similar study (Acalovschi et al., 2002). Immediately before meal ingestion, gallbladder dimensions in three orthogonal planes were obtained in supine position to calculate the fasting gallbladder ellipsoid volume. GBCI was calculated using change in volume divided by original fasting volume multiplied by 100. Immediately after meal ingestion, the subject laid on the couch for postprandial measurements.

Established protocols were used to measure meal stimulated gallbladder emptying (Hussaini et al., 1996). The maximum length, width and height of the gallbladder were obtained in supine position as previously documented (Ugwu, 2006, 2008; Ugwu and Erondu,

Table 1. Comparative stimulation of gallbladder motility after administration of erythromycin and azithromycin.

Parameter	T_5	T_{10}	T_{15}	T_{20}	T_{25}	T_{30}	T_{35}	T_{40}
Mean GBCI (Erythromycin + fatty meal)	39.18	46.81	64.23	67. 58	72.4	70.4	83.29	72.93
Mean GBCI (Azithromycin + fatty meal)	18.53	38.97	59.46	67.43	76.5	79.9	80.75	83.12
P	0.00	0.049	0.043	0.95	0.04	0.01	0.014	0.000

GBC1: Gallbladder contraction index in percentage; Tx: time at which GBC1 was obtained in minutes.

2009). The gallbladder volume and emptying were assessed by the ellipsoid method (Dodds et al., 1986). Serial volume measurements were obtained immediately before the test meal, 5, 10, 15, 20, 25, 30, 35 and 40 min after the test meal. The 40 min adopted in this study have been used in a previous study (Elrichman et al., 2007). Subjects were allowed to sit down in between procedures but lay down (supine) during ultrasonography of the gallbladder. All observations were made by an imaging scientist experienced in gut sonography. The percentage changes in gallbladder sizes using the fasting volume as initial volume at every point were calculated as the gallbladder contraction indices (ejection fractions). The subjects ages were obtained, heights were measured on a calibrated vertical wall and weights obtained on a weighing scale (model H 89 LT Blue).

Statistical analyses were conducted using SPSS software version 16.0 (SPSS INC; Chicago, Illinois, USA). Gaussian responses of gallbladder contraction indices (GBCIs) were conducted using Kolmogorov-Smirnoff test. Paired (repeated measure) t-test were conducted to assess the differences in mean values of GBCIs at erythromycin and azithromycin phases. $P<0.005$ was used as the criteria of statistical significance.

RESULTS

Twenty four males enrolled into and completed the study. Their ages ranged from 27 to 40 years, while their weight ranged from 55 to 69 kg.

Table 1 shows a comparative stimulation of gallbladder motility after administration of erythromycin and azithromycin.

In the first 15 min, erythromycin showed a significantly higher GBCI. This was not sustained after the 15th minute as the GBCI values in the 20th minute with both erythromycin and azithromycin were not significantly higher than GBCI values with erythromycin, but this was not sustained at the 35th minute as GBCI values were higher with erythromycin (Table 1). On the 40th minute, the GBCI values were higher with azithromycin.

DISCUSSION

Erythromycin is a prokinetic motilin analogue. Its treatment for animals on high cholesterol diet restored gallbladder contractility and reduced crystal formation (Xu et al., 1998). The result of this study indicated that erythromycin significantly enhanced gallbladder contractility compared to and better than azithromycin, having shown greater impact on GBCI at more stages (Table 1) than azithromycin. This enhancement of gallbladder motility by erythromycin has been reported previously (Xu et al., 1998; Urbain et al., 1990). Hence, from efficacy point of view, erythromycin should be the preferred prokinetic macrolide to azithromycin, but from the tolerance point of view, azithromycin which showed cholestecytokinetic superiority in few stages could be used.

This novel finding indicates that azithromycin could be used as an alternative cholecystokinetic agent for the treatment of gallbladder dysmotility and perhaps cholestasis which can predispose to stone growth. This comparison was done for the purpose of assessing whether azithromycin can be used as a substitute to erythromycin in patients with known cardiac disease (Prolonged QT) or in patients on concomitant medications which also interact with the cytochrome P 450 enzymes like erythromycin does. Patients with unexplained abdominal pain are often on antidepressants, most of which interact with the CYP3A isoenzymes as erythromycin would induce them. In contrast, azithromycin does not inhibit the CYP3A isoenzymes.

Another benefit in using azithromycin is that it reaches higher intracellular concentrations, thus increasing both its duration of action and its efficacy (Moshiree et al., 2010). Furthermore, azithromycin is absorbed rapidly with food, increasing its absorption so that it can be taken with or without food. Moreover, in contrast to erythromycin, azithromycin has higher oral bioavailability. This bioavaibility gives azithromycin an extensive distribution throughout the body with high tissue levels and at the same time poor central nervous system penetration.

Finally, the long half-life of azithromycin (up to 68 h) can potentially allow for easier administration due to long duration of effect (Moshiree, 2010). Azithromycin could be dosed once daily, as a result, as opposed to four times daily administration of oral erythromycin. This once daily may also improve patient compliance with taking the medication.

Future studies in this area involving chronic dosing of these drugs would further underpin their actual clinical value in cholecystokinesis and GBCI for $t > 40$ min should be ascertained using similar methodology with blinding of subjects and the sonographers conducting the study. On efficacy grounds, erythromycin is suggested as a preferred cholecystokinetic drug, but from tolerance point of view, azithromycin should be used.

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