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In vitro Interaction of Erythromycin and Polyvalent Metallic Ions (antacid) against Clinical Bacterial Isolates

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Abstract: Background: Several *in vivo* studies indicated that interactions between antacids and some therapeutic agents could result in treatment failures. Most of these studies have failed to take cognizance of the *in vitro* effects of these interactions on infectious agents. Hence, this study investigated the interactions between erythromycin and polyvalent metallic ions and the effects of combining them against some clinical bacterial isolates *in vitro*. **Methods:** Different concentrations of erythromycin ranging between 2.5 and 30.0 μg mL^{-1} and their combination with different concentrations, 0.05-1.0 mg mL^{-1}, of polyvalent metallic ions were tested against some clinical bacterial isolates. After the incubation period, inhibition zones from erythromycin alone and its combination with polyvalent metallic ions were measured and subjected to statistical analysis. **Result:** There was antagonistic interaction between erythromycin and the polyvalent metallic ions resulting in a significant reduction in the antibacterial activity of erythromycin on the clinical isolates. The possibility of bacterial resistant development as a result of combining these two drugs was observed while treatment failure was suggested by the associated reduction of the inhibition zones. **Conclusion:** In conclusion, combining erythromycin and polyvalent metallic ions should be discouraged in chemotherapy since the observed antagonistic interaction could result in development of bacterial resistance or treatment failure.

Key words: Erythromycin, macrolides, antibacterial activity, chemotherapy

INTRODUCTION

Macrolides are a group of polyketides whose activity is derived from the presence of a large macrocyclic lactone ring (Saleem *et al*., 2010). They are grouped according to the number of atoms comprising the lactone ring characteristically differentiating them chemically and biologically (Shryock *et al*., 1998). They constitute a group of 12 to 16-membered lactone rings substituted with one or more amino sugar residues (Anadon and Reeve-Johnson, 1999). While most macrolides are bacteriostatic and can be bactericidal at higher concentrations, new classes of macrolide antibiotics known as ketolides show improved activity against organisms that has developed resistance to previously used macrolide (Garza-Ramoz *et al*., 2001). Their efficacy is, however, typically greater for Gram positive bacteria than for Gram negative bacteria (Swords and Rubin, 2003).

Although allergy to macrolides is extremely rare (Demoly *et al*., 2000), macrolides are among the best tolerated antibacterial agents (Bryskier and Labro, 1994). They inhibit bacterial protein synthesis by binding to the ribosome (Garza-Ramoz *et al*., 2001; Omura, 2002), ribosome assembly (Chittum and Champney, 1995), peptide elongation on the ribosome (Lovmar *et al*., 2004) and translocation of peptidyl-tRNA from the acceptor to the donor site (Takashima, 2003). Macrolide antibiotics have peptide hormones activities and immunodulatory or anti-inflammatory activities (Abe *et al*., 2000; Labro and Abdelghaffar, 2001).

Erythromycin is the first macrolide to be used clinically, isolated from the metabolic products of a strain of *Streptocmyces erythreus* in 1952 (Parsad *et al*., 2003), represented the first generation of 14-membered-ring macrolide (Garza-Ramoz *et al*., 2001) with ten asymmetric centers and two sugars (L-cladinose and D-desoamine). After its oral or parenteral administration, erythromycin diffuses readily into intracellular fluids and is actively concentrated intracellularly by polymorphonuclear leukocytes and alveolar macrophages (Washington and Sutter, 1980).

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While the selection of an antimicrobial treatment regimen is based on the nature of the infection, the identity and susceptibility pattern of the infecting organisms as well as the pharmacokinetics and pharmacodynamics of the antibacterial drugs, the number of antibiotics available to the clinician for treatment of infectious diseases continues to increase. Erythromycin is an effective drug for many acute orofacial infections (Pallasch, 1997). Erythromycin is used to treat infections caused by gram-positive bacteria, *Mycoplasma* species, *Legionella* species, *Chlamydia* species and *Haemophilus influenza* (Fraser *et al*., 1977; Ianaro *et al*., 2000). Members of the family Enterobacteriaceae and *Pseudomonas aeruginosa* are generally resistant (Rozgonyi *et al*., 1989). While erythromycin exhibits prokinetic effects (Roussel *et al*., 2000; Curry *et al*., 2001) reversing gastrostatic actions of the antimotion sickness drugs (Stewart *et al*., 2000), the pharmacokinetics and adverse events profile of erythromycin initially limited its use to an alternative agent for patients with allergy to beta-lactam agents (Blondeau *et al*., 2002). It is frequently the first alternative in patients allergic to penicillin (Parsad *et al*., 2003).

Several clinically significant drug interactions have been identified since the approval of erythromycin (Pai *et al*., 2000). Erythromycin caused increase in the apparent volume of distribution of theophylline (Branigan *et al*., 1981) and inhibited carbazepine oxidation (Turner and Renton, 1989). It has been reported to cause a significant change in the pharmacokinetics and pharmacodynamics of midazolam (Zimmermann *et al*., 1996). Its co-administration with nitrazepam is of little clinical significance (Luurila *et al*., 1995). While several studies indicated that erythromycin interact with different drug compounds, there is a dearth of information on the interaction between erythromycin and polyvalent metallic ion *in vivo* and *in vitro* against bacterial isolates. Hence, this study was designed to investigate the *in vitro* effects of polyvalent metallic ion on the antibacterial activity of erythromycin.

MATERIALS AND METHODS

This study was conducted in the Department of Biosciences and Biotechnology, Babcock University, Ilishan Remo, Nigeria. Erythromycin powder was obtained from Fidson Pharmaceutical Company, Nigeria while the polyvalent metallic ions in the form of antacid tablets containing magnesium trisilicate-250 mg and aluminum hydroxide-120 mg were obtained from Dana Pharmaceuticals PVT. Ltd, Ambernath, India. The clinical isolates were obtained from the Obafemi Awolowo University Teaching Hospital, Ile-Ife, Osun State, Nigeria.

Preparation of drug solutions: Stock solution of erythromycin was prepared according to the NCCLS guidelines or manufacturer's recommendations (NCCLS, 1997). The average weight of the polyvalent metallic ions was obtained and a known weight containing one milligram of the powder was dissolved in 10 mL of sterile distilled water to form the initial stock solution. From the stock solutions, different concentrations of erythromycin (2.5-30.0) μg mL^{-1} and magnesium-aluminum hydroxide (0.05-1.0) μg mL^{-1} were prepared and used for the assay. Stock solutions of erythromycin and antacid were stored in the freezer at -20°C till used.

Clinical isolates: The clinical strains of bacteria used in this study included *Streptococcus pyogenes* (4 strains), *Haemophilus influenzae* (1 strain), *Staphylococcus aureus* (2 strains) *and Escherichia coli* (1 strain). They were identified and confirmed using morphological, microscopy and biochemical tests following standard procedures described by Cowan and Steel (1974) and Cheesborough (2006). The bacteria were grown in nutrient broth (Lab M Limited, UK) at 37°C and maintained on nutrient agar (Lab M Limited, UK) slants at 4°C. The susceptibility screening of the test bacteria to erythromycin alone and its combination with the polyvalent metallic ions was performed by a standard agar dilution technique (Washington and Wilson, 1985) with Mueller Hinton agar (Lab. M; International Diagnostic Group Plc., Lancashire, UK) as modified by Irobi *et al*. (1996).

All the data were subjected to one way Analysis of Variance (ANOVA) and the mean values were separated at ($p<0.05$) using Duncan's Multiple Range Test. The one way ANOVA test was used to determine if there was any statistically significant difference in the diameter of the inhibition zones obtained from the antibiotic alone and those of its combination with polyvalent metallic ions. All statistical analyses were done using SAS (1999) model.

RESULTS

The *in vitro* susceptibility of bacterial species to erythromycin alone and its combination with polyvalent metallic ions was investigated in this study. The Average Inhibition Zones (AZIs) of each test organism to erythromycin alone and its combination with polyvalent metallic ions were as present in Table 1-8. In these tables the first column represented different concentrations of erythromycin alone while the first row represented different concentrations of the polyvalent metallic ions. While the second column presented the AIZs produced by erythromycin alone, other columns presented the AIZs resulting from the interaction between the two agents.

Table 1: Inhibition zones of erythromycin and its combination with polyvalent metallic ions against *Strep. Pyogenes* STPI

	Concentrations of polyvalent metallic ions (μg mL^{-1})					
Concentrations of erythromycin (μg mL^{-1})	0.0	0.05	0.25	0.5	0.75	1.0
2.5	23.0±0.10	[a]20.0±0.10^{e}	21.0±0.10^{b}	19.0±0.10^{d}	20.0±0.10^{c}	20.0±0.10^{c}
5.0	25.0±0.10^{a}	22.0±0.10^{c}	22.0±0.10^{c}	23.0±0.10^{b}	22.0±0.10^{c}	22.0±0.10^{c}
7.5	25.0±0.10^{a}	24.0±0.10^{b}	22.0±0.10^{c}	20.0±0.10^{d}	22.0±0.10^{c}	22.0±0.10^{c}
10.0	27.0±0.10^{a}	25.0±0.10^{b}	23.0±0.10^{d}	25.0±0.10^{b}	24.0±0.10^{c}	24.0±0.10^{c}
15.0	28.0±0.10^{a}	24.0±0.10^{c}	24.0±0.10^{c}	22.0±0.10^{d}	24.0±0.10^{c}	25.0±0.10^{b}
20.0	30.0±0.10^{a}	24.0±0.10^{d}	27.0±0.10^{b}	25.0±0.10^{c}	24.0±0.10^{d}	24.0±0.10^{d}
25.0	30.0±0.10^{a}	27.0±0.10^{b}	26.0±0.10^{c}	27.0±0.10^{b}	25.0±0.10^{d}	24.0±0.10^{e}
30.0	30.0±0.10^{a}	27.0±0.10^{b}	25.0±0.10^{e}	25.0±0.10^{e}	25.0±0.10^{e}	25.0±0.10^{e}

The average inhibition zones with different superscript along the same row are significantly different ($p<0.05$)

Table 2: Inhibition zones of erythromycin and its combination with polyvalent metallic ions against *Strep. pyogenes* STP3

	Concentrations of polyvalent metallic ions (μg mL^{-1})					
Concentrations of erythromycin (μg mL^{-1})	0.0	0.05	0.25	0.5	0.75	1.0
2.5	22.0±0.10^{a}	17.0±0.10^{b}	17.0±0.10^{b}	12.0±0.10^{d}	13.0±0.10^{c}	13.0±0.10^{c}
5.0	23.0±0.10^{a}	18.0±0.10^{b}	16.0±0.10^{c}	15.0±0.10^{d}	16.0±0.10^{c}	14.0±0.10^{e}
7.5	22.0±0.10^{a}	17.0±0.10^{b}	15.0±0.10^{d}	15.0±0.10^{d}	16.0±0.10^{c}	15.0±0.10^{d}
10.0	24.0±0.10^{a}	21.0±0.10^{b}	17.0±0.10^{c}	16.0±0.10^{d}	16.0±0.10^{d}	15.0±0.10^{f}
15.0	25.0±0.10^{a}	22.0±0.10^{b}	18.0±0.10^{d}	16.0±0.10^{e}	20.0±0.10^{c}	15.0±0.10^{f}
20.0	27.0±0.10^{a}	23.0±0.10^{b}	19.0±0.10^{d}	17.0±0.10^{e}	20.0±0.10^{c}	15.0±0.10^{f}
25.0	25.0±0.10^{a}	23.0±0.10^{b}	20.0±0.10^{d}	19.0±0.10^{e}	21.0±0.10^{c}	16.0±0.10^{f}
30.0	25.0±0.10^{a}	24.0±0.10^{b}	18.0±0.10^{e}	20.0±0.10^{d}	21.0±0.10^{c}	13.0±0.10^{f}

The average inhibition zones with different superscript along the same row are significantly different ($p<0.05$)

Table 3: Inhibition zones of erythromycin and its combination with polyvalent metallic ions against *Strep. pyogenes* STP5

	Concentrations of polyvalent metallic ions (μg mL^{-1})					
Concentrations of erythromycin (μg mL^{-1})	0.0	0.05	0.25	0.5	0.75	1.0
2.5	21.0±0.10^{a}	18.0±0.10^{c}	18.0±0.10^{c}	18.0±0.10^{c}	20.0±0.10^{b}	18.0±0.10^{c}
5.0	23.0±0.10^{a}	20.0±0.10^{c}	19.0±0.10^{d}	20.0±0.10^{c}	21.0±0.10^{b}	21.0±0.10^{b}
7.5	23.0±0.10^{a}	21.0±0.10^{c}	20.0±0.10^{d}	22.0±0.10^{b}	21.0±0.10^{c}	21.0±0.10^{c}
10.0	25.0±0.10^{a}	24.0±0.10^{b}	22.0±0.10^{d}	22.0±0.10^{d}	22.0±0.10^{d}	23.0±0.10^{c}
15.0	27.0±0.10^{a}	25.0±0.10^{b}	24.0±0.10^{c}	23.0±0.10^{d}	19.0±0.10^{e}	27.0±0.10^{a}
20.0	29.0±0.10^{a}	26.0±0.10^{b}	25.0±0.10^{c}	24.0±0.10^{d}	19.0±0.10^{f}	21.0±0.10^{e}
25.0	29.0±0.10^{a}	27.0±0.10^{b}	26.0±0.10^{c}	24.0±0.10^{d}	20.0±0.10^{f}	22.0±0.10^{e}
30.0	30.0±0.10^{a}	26.0±0.10^{b}	26.0±0.10^{b}	25.0±0.10^{c}	21.0±0.10^{d}	21.0±0.10^{d}

The average inhibition zones with different superscript along the same row are significantly different ($p<0.05$)

Table 4: Inhibition zones of erythromycin and its combination with polyvalent metallic ions *Strep. pyogenes* STP8

	Concentrations of polyvalent metallic ions (μg mL^{-1})					
Concentrations of erythromycin (μg mL^{-1})	0.0	0.05	0.25	0.5	0.75	1.0
2.5	19.0±0.10^{a}	14.0±0.10^{e}	15.0±0.10^{b}	15.0±0.10^{b}	15.0±0.10^{b}	15.0±0.10^{b}
5.0	20.0±0.10^{a}	18.0±0.10^{b}	18.0±0.10^{b}	18.0±0.10^{b}	16.0±0.10^{c}	18.0±0.10^{b}
7.5	21.0±0.10^{a}	19.0±0.10^{b}	19.0±0.10^{b}	17.0±0.10^{d}	18.0±0.10^{c}	18.0±0.10^{c}
10.0	25.0±0.10^{a}	20.0±0.10^{b}	19.0±0.10^{c}	18.0±0.10^{d}	19.0±0.10^{c}	19.0±0.10^{c}
15.0	25.0±0.10^{a}	22.0±0.10^{b}	22.0±0.10^{b}	21.0±0.10^{c}	19.0±0.10^{d}	19.0±0.10^{d}
20.0	26.0±0.10^{a}	21.0±0.10^{b}	20.0±0.10^{c}	19.0±0.10^{d}	20.0±0.10^{c}	21.0±0.10^{b}
25.0	24.0±0.10^{a}	22.0±0.10^{c}	23.0±0.10^{b}	20.0±0.10^{e}	20.0±0.10^{e}	21.0±0.10^{d}
30.0	28.0±0.10^{a}	23.0±0.10^{b}	21.0±0.10^{c}	19.0±0.10^{e}	20.0±0.10^{d}	20.0±0.10^{d}

The average inhibition zones with different superscript along the same row are significantly different ($p<0.05$)

AIZs with different superscript along each row indicated that resultant AIZs from the combination of erythromycin and polyvalent metallic ions were significantly different when compared with AIZs produced when each organisms was subjected to erythromycin alone.

The obtained results indicated a significant decrease in the antibacterial activity of erythromycin when combined with different concentrations of the polyvalent metallic ions. Inhibition zones obtained from their combinations were smaller than those obtained from erythromycin alone. The polyvalent metallic ions exhibited varied degree of inhibitions on the antibacterial activity of erythromycin indicating that their interactions were not concentration dependent. While resistant colonies were not observed within the inhibition zones from erythromycin, fussy inhibition zones observed around clear zones of inhibition from the combination indicated that combining the two agents could result in the development of bacterial resistance. Statistically, the

Table 5: Inhibition zones of erythromycin and its combination with polyvalent metallic ions against *Escherichia coli* Ecl10

	Concentrations of polyvalent metallic ions (μg mL^{-1})					
Concentrations of erythromycin (μg mL^{-1})	0.0	0.05	0.25	0.5	0.75	1.0
2.5	18.0±0.10^{a}	18.0±0.10^{a}	18.0±0.10^{a}	16.0±0.10^{b}	13.0±0.10^{d}	14.0±0.10^{c}
5.0	19.0±0.10^{c}	20.0±0.10^{b}	17.0±0.10^{d}	21.0±0.10^{a}	15.0±0.10^{e}	15.0±0.10^{e}
7.5	20.0±0.10^{b}	21.0±0.10^{a}	18.0±0.10^{c}	20.0±0.10^{b}	15.0±0.10^{d}	15.0±0.10^{d}
10.0	22.0±0.10^{a}	22.0±0.10^{a}	20.0±0.10^{c}	21.0±0.10^{b}	17.0±0.10^{d}	16.0±0.10^{e}
15.0	25.0±0.10^{a}	18.0±0.10^{e}	20.0±0.10^{b}	17.0±0.10^{d}	15.0±0.10^{f}	16.0±0.10^{e}
20.0	23.0±0.10^{a}	19.0±0.10^{e}	21.0±0.10^{b}	19.0±0.10^{e}	18.0±0.10^{d}	18.0±0.10^{d}
25.0	25.0±0.10^{a}	21.0±0.10^{e}	22.0±0.10^{b}	20.0±0.10^{d}	19.0±0.10^{e}	19.0±0.10^{e}
30.0	28.0±0.10^{a}	20.0±0.10^{e}	22.0±0.10^{b}	20.5±0.60^{e}	20.0±0.10^{e}	20.0±0.10^{e}

The average inhibition zones with different superscript along the same row are significantly different ($p<0.05$)

Table 6: Inhibition zones of erythromycin and its combination with polyvalent metallic ions against *Haemophilus influenzae*

	Concentrations of polyvalent metallic ions (μg mL^{-1})					
Concentrations of erythromycin (μg mL^{-1})	0.0	0.05	0.25	0.5	0.75	1.0
2.5	0.0±0.00^{a}	0.0±0.00^{a}	0.0±0.00^{a}	0.0±0.00^{a}	0.0±0.00^{a}	0.0±0.00^{a}
5.0	0.0±0.00^{a}	0.0±0.00^{a}	0.0±0.00^{a}	0.0±0.00^{a}	0.0±0.00^{a}	0.0±0.00^{a}
7.5	0.0±0.00^{a}	0.0±0.00^{a}	0.0±0.00^{a}	0.0±0.00^{a}	0.0±0.00^{a}	0.0±0.00^{a}
10.0	14.0±0.10^{a}	12.0±0.10^{b}	9.0±0.10^{e}	11.0±0.10^{c}	9.0±0.10^{e}	10.0±0.10^{e}
15.0	18.0±0.10^{a}	15.0±0.10^{e}	17.0±0.10^{b}	12.0±0.10^{e}	13.0±0.10^{d}	12.0±0.10^{e}
20.0	19.0±0.10^{a}	17.0±0.10^{b}	16.0±0.10^{c}	15.0±0.10^{d}	17.0±0.10^{b}	14.0±0.10^{e}
25.0	20.0±0.10^{a}	19.0±0.10^{b}	20.0±0.10^{a}	16.0±0.10^{d}	17.0±0.10^{c}	14.0±0.10^{e}
30.0	21.0±0.10^{a}	18.0±0.10^{e}	20.0±0.10^{b}	16.0±0.10^{d}	14.0±0.10^{e}	14.0±0.10^{e}

The average inhibition zones with different superscript along the same row are significantly different ($p<0.05$)

Table 7: Inhibition zones of erythromycin and its combination with polyvalent metallic ions against *S. aureus* S887

	Concentrations of polyvalent metallic ions (μg mL^{-1})					
Concentrations of erythromycin (μg mL^{-1})	0.0	0.05	0.25	0.5	0.75	1.0
2.5	13.0±0.10^{d}	13.0±0.10^{d}	16.0±0.10^{a}	15.0±0.10^{b}	14.0±0.10^{c}	14.0±0.10^{c}
5.0	16.0±0.10^{b}	17.0±0.10^{a}	17.0±0.10^{a}	13.0±0.10^{d}	14.0±0.10^{c}	13.0±0.10^{d}
7.5	19.0±0.10^{a}	19.0±0.10^{a}	18.0±0.10^{b}	18.0±0.10^{b}	15.0±0.10^{c}	15.0±0.10^{c}
10.0	20.0±0.10^{a}	20.0±0.10^{a}	19.0±0.10^{b}	17.0±0.10^{c}	17.0±0.10^{c}	15.0±0.10^{d}
15.0	21.0±0.10^{a}	18.0±0.10^{b}	18.0±0.10^{b}	18.0±0.10^{b}	18.0±0.10^{b}	16.0±0.10^{c}
20.0	22.0±0.10^{a}	19.0±0.10^{b}	19.0±0.10^{b}	18.0±0.10^{c}	19.0±0.10^{b}	18.0±0.10^{c}
25.0	25.0±0.10^{a}	20.0±0.10^{e}	22.0±0.10^{b}	19.0±0.10^{d}	18.0±0.10^{e}	19.0±0.10^{d}
30.0	26.0±0.10^{a}	20.0±0.10^{e}	22.0±0.10^{b}	20.0±0.10^{e}	18.0±0.10^{d}	20.0±0.10^{e}

The average inhibition zones with different superscript along the same row are significantly different ($p<0.05$)

Table 8: Inhibition zones of erythromycin and its combination with polyvalent metallic ions against *S. aureus* S253

	Concentrations of polyvalent metallic ions (μg mL^{-1})					
Concentrations of erythromycin (μg mL^{-1})	0.0	0.05	0.25	0.5	0.75	1.0
2.5	18.0±0.10^{b}	14.0±0.10^{e}	15.0±0.10^{d}	18.0±0.10^{b}	20.0±0.10^{a}	17.0±0.10^{c}
5.0	19.0±0.10^{b}	17.0±0.10^{d}	19.0±0.10^{b}	19.0±0.10^{b}	21.0±0.10^{a}	18.0±0.10^{c}
7.5	20.0±0.10^{d}	22.0±0.10^{b}	18.0±0.10^{e}	21.0±0.10^{c}	23.0±0.10^{a}	20.0±0.10^{d}
10.0	22.0±0.10^{b}	20.0±0.10^{d}	18.0±0.10^{e}	21.0±0.10^{c}	24.0±0.10^{a}	22.0±0.10^{b}
15.0	25.0±0.10^{a}	23.0±0.10^{b}	19.0±0.10^{e}	19.6±0.50^{e}	21.0±0.10^{c}	20.0±0.10^{d}
20.0	26.0±0.10^{a}	25.0±0.10^{b}	20.0±0.10^{f}	21.0±0.10^{e}	23.0±0.10^{c}	22.0±0.10^{d}
25.0	27.0±0.10^{a}	26.0±0.10^{b}	21.0±0.10^{f}	23.0±0.10^{d}	24.0±0.10^{c}	22.0±0.10^{e}
30.0	27.0±0.10^{a}	25.0±0.10^{b}	22.0±0.10^{e}	24.0±0.10^{c}	23.0±0.10^{d}	23.0±0.10^{d}

The average inhibition zones with different superscript along the same row are significantly different ($p<0.05$)

AZIs with different superscript in the same row indicated that there are significant differences between the activity of erythromycin alone and its combinations with the polyvalent metallic ions.

DISCUSSION

In this study, the bacteria exhibited different susceptibilities to different concentrations of erythromycin used. From the obtained result, it is quite apparent that the availability of erythromycin was decreased *in vitro* in the presence of the polyvalent metallic ions thereby resulting in the decrease in the antibacterial activity of this antibiotic. This is contrary to the earlier report of Sultana *et al*. (2005) indicating that antimicrobial activity of complexes of erythromycin increases with respect to erythromycin drug.

In vivo studies indicated that several antibiotics show significant interactions when they are given orally concomitantly with antacids. The coadministration of

antibiotics and antacids significantly reduce the oral absorption of antibiotics, resulting in a loss of activities. This was demonstrated for tetracyclines (Neuvonen, 1976; Deppermann *et al*., 1989) and fluoroquinolones such as amifloxacin, ciprofloxacin, norfloxacin and ofloxacin (Lode, 1988; Stroshane *et al*., 1989; Gugler and Allgayer, 1990; Mizuki *et al*., 1996). *In vivo* co-administration of erythromycin with antacid had no effect on the peak serum concentration (Cmax), total area under the concentration-time curve (AUC), or time to peak concentration (Tmax) of erythromycin (Webpage). For tetracycline, the proposed mechanism was the pH-dependent formation of chelates with metal ions, such as Fe^{2+}, Al^{3+}, Ca^{2+} and Mg^{2+}, which leads to formation of poorly soluble complexes that are not well absorbed from the gut lumen (Chin and Lach, 1975; Arayne *et al*., 2005). For fluoroquinolones, it was the formation of insoluble chelates between the 3-carbonyl and 4-oxo groups of the fluoroquinolones and aluminum and magnesium ions. For erythromycin, the mechanism of interaction is unknown.

The interaction between erythromycin and polyvalent metallic ions obtained in this study agreed with the earlier study that reported interactions of erythromycin with antacids such as aluminum hydroxide, aluminum trisilicate, magnesium oxide, magnesium trisilicate and dimethylpolysiloxane (Hedrick *et al*., 1983). Arayne and Sultana (1993), also reported retardation of *in vitro* dissolution of erythromycin in the presence of antacids. This report showed that the inability of erythromycin to dissolve in the presence of antacids or formation of insoluble complexes *in vitro* may have suggested the rationale for the reduction in the antibacterial activities of erythromycin observed in this study.

In conclusion, while the mechanism of interaction of erythromycin and antacids is unknown, there are limited data on the interactions between these drugs. This study indicated antagonistic interaction between erythromycin and polyvalent metallic ions which could result in development of resistant organisms or treatment failure if erythromycin is used in chemotherapy immediately after the ingestion of the antacid. Further studies on the mechanism of interaction between erythromycin and magnesium-aluminum hydroxide are, however, suggested.

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