



(RESEARCH ARTICLE)



In vitro effects of quinine on the antibacterial activity of erythromycin against bacteria of clinical relevance

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GSC Biological and Pharmaceutical Sciences, 2021, 14(02), 077–086

Publication history: Received on 12 January 2021; revised on 08 February 2021; accepted on 10 February 2021

Article DOI: <https://doi.org/10.30574/gscbps.2021.14.2.0033>

Abstract

The study investigated the *in vitro* effects of quinine on the antibacterial activity of erythromycin for possible interactions. The antibacterial activities of each drug and their combinations were investigated by agar diffusion, agar and macrobroth dilution methods. While 100 μ l of 1000 μ g/ml of erythromycin produced inhibition zones ranging between 13 and 31 ± 1.0 mm in all the isolates except *K. pneumoniae* and *P. aeruginosa* ATCC 19582, combining the highest concentration of erythromycin with 35 μ g/ml of quinine produced inhibition zones ranging between 14 and 34 ± 1.0 mm with the exception of *S. flexneri* KZN. Though quinine had no antibacterial effects on the isolates, erythromycin was effective at minimum inhibitory concentrations (MICs) ranging between 25 and 100 μ g/ml while their combinations resulted in reduction of MICs of most of the isolates to 12.5 μ g/ml except those against *A. calcaocticus anitratus* CSIR, *Ps. aeruginosa* ATCC 15442, *P. shigelloides* ATCC 51903, *A. hydrophila* ATCC 35654, *Ps. aeruginosa* ATCC 19582 and *E. faecalis* KZN that remained unchanged in agar dilution. While the MICs of erythromycin ranged between 25 and 50 μ g/ml, the MICs of this antibiotic was reduced to concentrations ranging between 12.5 and 50 μ g/ml indicating 50% to 75% in the presence of quinine. The combination of erythromycin and quinine, *in vitro*, resulted in synergistic (50%), additive/indifference (44.44%) and antagonistic (11.11%) interactions while quinine at concentrations lower than plasma quinine concentrations was inhibitory to the antibacterial activity of erythromycin. The synergistic effect may serve as remedy for bacterial infections in which the test bacteria have been implicated.

Keywords: Antibacterial combination; Erythromycin; Resistance; Synergism; Quinine

1. Introduction

The increasing prevalence of drug-resistant bacteria as well as increased means of gaining resistance has made it crucial to explore and find alternative to antibacterial therapies. Consequently, drugs are combined to produce pharmacological effectiveness better than the anticipated effects of the drugs involved when used alone. Though the uses of drugs from one or more groups in combinations have been with the expectation of achieving therapeutic efficacies, the outcomes have not been without interactions. Drug interactions occur when the effect and/or concentration of a drug is modified by another substance in a concomitant treatment [1,2]. While a drug-drug interaction is a pharmacodynamic or pharmacokinetic influence of one drug on another to reduce the efficacy of one or both of the interacting drugs or to exacerbate other adverse effects of each other in nature [3], interactions may result in negative long-term outcomes and increased healthcare utilization and costs [4]. On the other hand, drug combinations resulting in synergistic interactions may increase efficacy while decreasing cytotoxicity by minimizing the required therapeutic doses [5].

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Drug-drug interactions are actually quite common-place [6,7]. Although the incidence of adverse drug interactions caused by drug-drug interactions is modest [8,9], they are severe and, in most cases, lead to hospitalization [10]. They pose a risk of serious side effects to patients and are, also, among the leading cause of patient morbidity and mortality [11,12]. Although the percentage of potential drug-drug interactions resulting in adverse drug interactions ranged between 0% and 60% [13,14], polypharmacy resulting in drug-drug interactions account for 2.8% of hospital admission [15] and 3 – 5% of all in-hospital medication errors [16].

Erythromycin, the first macrolide antibiotic to be used clinically, is a metabolic product of *Streptococcus erythreus* [17]. It has chemical formula $C_{37}H_{67}O_{13}$ [18], exhibit prokinetic effect [19] and reverse gastrostatic actions of antimotility sickness drugs [20]. Structurally, it contains a 14-membered lactone ring with ten asymmetric centres and two sugars (L-cladinose and D-desosamine) making it a compound very difficult to produce by synthetic methods due to the presence of ten stereo-specific carbons and several points of distinct substitution [21]. Erythromycin, acting as a motilin receptor agonist [22] and metabolized by enzymes of the cytochrome P450 system [23], is often prescribed to people allergic to penicillins [17] and not recommended when using clindamycin-containing products. The simultaneous use of two erythromycin derivatives should be avoided as they possess a common mechanism of action [24]. Its combination with other drugs showed inhibition of carbamazepine oxidation [25], changed pharmacokinetics and pharmacodynamics of midazolam [26] and had reduced antibacterial activity when combined with antacids [27]. While its *in vivo* interaction with quinine, a natural compound in *Cinchona* bark used in malaria endemic regions, against *Plasmodium falciparum* had been reported [28], there is a dearth of information on the *in vitro* influence of quinine on the antibacterial activity of erythromycin and possible interactions between the two drugs if co-administered in bacterial infections. This study, therefore, aimed at investigating the *in vitro* antibacterial activity of erythromycin alone and its combination with quinine for possible interactions which may be of clinically significant effect.

2. Material and methods

2.1. Bacterial culture and preparation of antibiotic solutions

The bacteria used in this study include *Micrococcus luteus*, *Pseudomonas aeruginosa* ATCC 15442, *Bacillus subtilis* KZN, *Plesiomonas shigelloides* ATCC 51903, *Aeromonas hydrophila* ATCC 35654, *Staphylococcus aureus* NCT 6571, *Escherichia coli* ATCC 25922, *Klebsiella pneumoniae* ATCC 10031, *Pseudomonas aeruginosa* ATCC 19582, *Klebsiella pneumoniae* ATCC 4352, *Proteus vulgaris* ATCC 6830, *Enterococcus faecalis* KZN, *Enterococcus faecalis* ATCC 29212, *Serratia marcescens* ATCC 9986, *Acinetobacter calcoaceticus anitratus* CSIR, *Shigella flexneri* ATCC 4352, *Enterococcus cloacae* ATCC 4352 and *Shigella sonnei* ATCC 29930. Pure antibiotic powders of erythromycin and quinine were used. The stock erythromycin and quinine solutions were prepared and dilutions made according to the manufacturer's recommendations.

2.2. Antibiotic susceptibility testing - agar diffusion method

Each bacterial strain's colony suspension was matched with 0.5 McFarland standards to give a resultant concentration of 1.5×10^7 cfu/ml. The antibiotic susceptibility testing was determined by swabbing the Mueller-Hinton agar (MHA) (Oxoids U.K) plates with the adjusted bacterial strains according to [29]. Agar wells were made with heat sterilized 6 mm cork borer before being filled with 100 μ l of 250, 500 and 1000 μ g/ml of erythromycin alone and 250 + 8.75, 500 + 17.5 and 1000 + 35 μ g/ml of erythromycin combined with quinine taking care not to allow spillage of the solutions onto the agar surface. The plates, in duplicate, were allowed to stand for 1 h before being incubated at 37°C for 24 h. After incubation, the diameter of the inhibition zones produced by the antibiotic alone and those of its combination with quinine were measured in millimetres with a transparent rule and interpreted using the CLSI zone diameter interpretative standards [29]. Synergism was considered when combinations exhibited inhibition zones increment of 0.5 mm above those produced by the erythromycin alone.

2.3. Antibiotic susceptibility testing - agar dilution method

For the agar dilution assay, different concentrations (0.390 - 400) μ g/ml of erythromycin and (0.093 - 200) μ g/ml of quinine and their combinations were prepared in sterile Mueller Hinton agar maintained at 50°C. The antibiotic containing molten agar were gently agitated before being poured into sterile petri plates and allowed to solidify after which they were streaked with different isolates adjusted to 10^6 cfu/ml and incubated at 37°C for 24 h. The lowest concentration of erythromycin alone and those of its combination with quinine inhibiting the growth of the isolates were taken as the minimum inhibitory concentration.

2.4. Determination of minimal inhibitory concentrations (MICs)

To determine the MICs of erythromycin and quinine, 100 μ l of each isolate was added to different concentrations (0.390 - 400) μ g/ml of erythromycin and (0.093 - 200) μ g/ml of quinine prepared by serial dilution in double strength Mueller Hinton broth. These concentration ranges were chosen on the basis that maximum macrolide serum concentrations ranged between 0.4 and 12 μ g/ml [30] and plasma quinine concentrations ranged between 8 and 15 μ g/ml [31]. To determine the effects of combining these drugs, each of the concentrations of the antibiotic and the quinine used in determining their MICs were combined before being inoculated with 100 μ l of each of the bacterial strains and incubated at 37°C for 24 h. Blank Mueller Hinton broth was used as negative control. The MIC was defined as the lowest dilution that showed no growth in the Mueller Hinton broth. When the MICs of erythromycin in combination equal its MIC when used alone, the interactions were considered additive/indifference. When the MICs of erythromycin in combination were lower than its MICs when used alone, the interactions were considered synergistic. When the MICs of erythromycin in combination were higher than its MICs when used alone, the interactions were considered antagonistic.

2.5. Determination of minimum bactericidal concentrations (MBCs)

The minimum bactericidal concentration (MBC) is identified by determining the lowest concentration of antibacterial agent that reduced the viability of the initial bacterial inoculum by $\geq 99.9\%$. The MBC assays were carried out as described by Cheesbrough [32]. Here, antibiotic-free nutrient agar plates were inoculated with one loopful of culture taken from each of the first three broth cultures that showed no growth and the first growth-containing tube in the MIC tubes. The MBC plates were incubated at 37°C for 24 h. After the incubation periods, the lowest concentrations of erythromycin alone and its combination with quinine that did not produce bacterial growth on the solid medium were regarded as their MBC values. This observation was matched with the MIC test tube that did not show evidence of growth after 48 h of incubation.

3. Results

In this study, the inhibition zones produced by the erythromycin alone and its combination with quinine showed a concentration dependent antibacterial activity. With the exception of *K. pneumoniae* ATCC 4352 and *P. aeruginosa* ATCC 19582 which had no inhibition zones from erythromycin alone, the inhibition zones produced by the erythromycin alone ranged between 13 ± 1.0 mm and 31 ± 1.0 mm from 100 μ l of 1000 μ g/ml. Combining the highest concentration of erythromycin with 35 μ g/ml, all the isolates had inhibition zones ranging between 14 ± 1.0 mm and 34 ± 1.0 mm exception *S. flexneri* KZN that was not susceptible. The interaction between erythromycin and quinine in combination were, therefore, considered synergistic. The drug combinations inhibited the tested organisms at high concentrations with *S. aureus* NCT 6571, *E. coli* ATCC 25922, *S. marcescens* ATCC 9986, *M. luteus*, *S. flexneri* KZN, *K. pneumoniae* ATCC 4352, *P. aeruginosa* ATCC 19582 and *E. faecalis* ATCC 29212 being the most resistant to erythromycin alone and its combination with 17.5 and 8.75 μ g/ml quinine respectively (Table 1).

Table 1 Zones of Inhibition (± 1.00 mm) produced by erythromycin alone and its combination with quinine

	Erythromycin			Quinine			Erythromycin + Quinine		
	1000	500	250	35	17.5	8.75	1000 + 35	500 + 17.5	250 + 8.75
	----- $\mu\text{g/ml}$ -----								
<i>Micrococcus luteus</i>	16 \pm 1.0	0	0	0	0	0	15 \pm 1.0	0	0
<i>Shigella flexneri</i> KZN	13 \pm 1.0	0	0	0	0	0	0	0	0
<i>Bacillus subtilis</i> KZN	14 \pm 1.0	11 \pm 1.0	0	0	0	0	15 \pm 1.0	11 \pm 1.0	0
<i>Enterococcus faecalis</i> KZN	24 \pm 1.0	21 \pm 1.0	19 \pm 1.0	0	0	0	24 \pm 1.0	22 \pm 1.0	20 \pm 1.0
<i>Proteus vulgaris</i> ATCC 6830	28 \pm 1.0	26 \pm 1.0	22 \pm 1.0	0	0	0	26 \pm 1.0	24 \pm 1.0	21 \pm 1.0
<i>Shigella sonnei</i> ATCC 29930	25 \pm 1.0	23 \pm 1.0	20 \pm 1.0	0	0	0	27 \pm 1.0	26 \pm 1.0	25 \pm 1.0
<i>Escherichia coli</i> ATCC 25922	15 \pm 1.0	0	0	0	0	0	14 \pm 1.0	0	0
<i>Staphylococcus aureus</i> NCT 6571	15 \pm 1.0	0	0	0	0	0	16 \pm 1.0	0	0
<i>Klebsiella pneumonia</i> ATCC 4352	0	0	0	0	0	0	14 \pm 1.0	0	0
<i>Klebsiella pneumoniae</i> ATCC 10031	31 \pm 1.0	27 \pm 1.0	25 \pm 1.0	0	0	0	34 \pm 1.0	28 \pm 1.0	26 \pm 1.0
<i>Enterococcus faecalis</i> ATCC 29212	15 \pm 1.0	0	0	0	0	0	16 \pm 1.0	0	0
<i>Enterobacter cloacae</i> ATCC 13047	31 \pm 1.0	30 \pm 1.0	28 \pm 1.0	0	0	0	34 \pm 1.0	29 \pm 1.0	25 \pm 1.0
<i>Serratia marcescens</i> ATTC 9986	15 \pm 1.0	0	0	0	0	0	16 \pm 1.0	0	0
<i>Aeromonas hydrophila</i> ATCC 35654	13 \pm 1.0	12 \pm 1.0	0	0	0	0	15 \pm 1.0	13 \pm 1.0	12 \pm 1.0
<i>Plesiomonas shigelloides</i> ATCC 51903	26 \pm 1.0	22 \pm 1.0	16 \pm 1.0	0	0	0	24 \pm 1.0	21 \pm 1.0	20 \pm 1.0
<i>Pseudomonas aeruginosa</i> ATCC 15442	17 \pm 1.0	15 \pm 1.0	13 \pm 1.0	0	0	0	18 \pm 1.0	16 \pm 1.0	13 \pm 1.0
<i>Pseudomonas aeruginosa</i> ATCC 19582	0	0	0	0	0	0	14 \pm 1.0	0	0
<i>Acinetobacter calcoocticus anitratus</i> CSIR	15 \pm 1.0	12 \pm 1.0	0	0	0	0	16 \pm 1.0	11 \pm 1.0	0

The agar dilution assay for determining the antibacterial effects of erythromycin alone and its combination with quinine showed that quinine had no antibacterial activity on the isolates. However, while the isolates were susceptible to erythromycin alone at concentrations ranging between 25 and 100 µg/ml, its combination with quinine resulted in reduction of most of the concentrations to 12.5 µg/ml except those against *A. calcaoeuticus anitratus* CSIR, *P. aeruginosa* ATCC 15442, *P. shigelloides* ATCC 51903, *A. hydrophila* ATCC 35654, *P. aeruginosa* ATCC 19582 and *E. faecalis* KZN that remained unchanged (Table 2).

Table 2 Antibacterial activity of erythromycin alone and its combination with quinine by agar dilution assay

Organisms	Erythromycin alone	Quinine alone	Erythromycin + Quinine
	----- (MIC µg/ml) -----		
<i>Micrococcus luteus</i>	37.5	0	12.5/3.125
<i>Shigella flexneri</i> KZN	25	0	12.5/3.125
<i>Bacillus subtilis</i> KZN	50	0	12.5/3.125
<i>Enterococcus faecalis</i> KZN	50	0	50/12.5
<i>Proteus vulgaris</i> ATCC 6830	37.5	0	12.5/3.125
<i>Shigella sonnei</i> ATCC 29930	37.5	0	12.5/3.125
<i>Escherichia coli</i> ATCC 25922	25	0	12.5/3.125
<i>Staphylococcus aureus</i> NCT 6571	25	0	12.5/3.125
<i>Klebsiella pneumonia</i> ATCC 4352	25	0	12.5/3.125
<i>Klebsiella pneumoniae</i> ATCC 10031	12.5	0	12.5/3.125
<i>Enterococcus faecalis</i> ATCC 29212	25	0	12.5/3.125
<i>Enterobacter cloacae</i> ATCC 13047	25	0	12.5/3.125
<i>Serratia marcescens</i> ATTC 9986	25	0	12.5/3.125
<i>Aeromonas hydrophila</i> ATCC 35654	100	0	100/25
<i>Plesiomonas shigelloides</i> ATCC 51903	100	0	100/25
<i>Pseudomonas aeruginosa</i> ATCC 15442	50	0	50/12.5
<i>Pseudomonas aeruginosa</i> ATCC 19582	100	0	100/25
<i>Acinetobacter calcaoeuticus anitratus</i> CSIR	50	0	50/12.5

The MICs of erythromycin against all the isolates ranged between 25 and 50 µg/ml while the MBCs ranged between 50 and 100 µg/ml. The quinine did not have any antibacterial effect on test bacterial isolates at the different dilution concentrations. On combining the erythromycin with quinine, the MICs of erythromycin was reduced by 50% to 75% and ranged between 12.5 and 50 µg/ml. The reduction in the MICs showed that the combination of erythromycin and quinine, *in vitro*, resulted in synergistic, additive/indifference and antagonistic interactions. In a descending order, 50% of the interactions were synergistic, 44.44% was additive/indifference and 11.11% was antagonistic. While these interactions occurred when 3.125 µg/ml and 6.25 µg/ml of quinine were combined with 12.5 µg/ml and 25 µg/ml respectively, combining 0.15 and 0.5 µg/ml of quinine with the different concentrations of erythromycin resulted in antagonistic interactions and showed that quinine at concentrations lower than the plasma quinine concentrations would be inhibitory to the antibacterial activity of erythromycin (Table 3).

Table 3 Minimum inhibitory and bactericidal concentrations of erythromycin alone and its combination with quinine

ORGANISM	Erythromycin alone		Quinine alone	Erythromycin + Quinine		Observed interactions	Erythromycin + quinine	Erythromycin + quinine
	MIC	MBC		MIC	MBC		200+0.15	200+0.5
				-----µg/ml-----			-----µg/ml-----	
<i>Micrococcus luteus</i>	25	100	0	25/6.25	100/25	Additive	100	200
<i>Shigella flexneri</i> KZN	50	100	0	50/12.5	100/25	Additive	200	100
<i>Bacillus subtilis</i> KZN	25	50	0	50/12.5	100/25	Antagonistic	200	200
<i>Enterococcus faecalis</i> KZN	25	50	0	25/6.25	100/25	Additive	200	200
<i>Proteus vulgaris</i> ATCC 6830	25	50	0	25/6.25	100/25	Synergy	200	200
<i>Shigella sonnei</i> ATCC 29930	50	100	0	50/12.5	100/25	Additive	200	<200
<i>Escherichia coli</i> ATCC 25922	25	50	0	12.5/3.125	50/12.5	Synergy	200	200
<i>Staphylococcus aureus</i> NCT 6571	50	100	0	12.5/3.125	50/12.5	Synergy	200	200
<i>Klebsiella pneumonia</i> ATCC 4352	50	100	0	25/6.25	100/25	Synergy	200	<200
<i>Klebsiella pneumoniae</i> ATCC 10031	25	50	0	25/6.25	100/25	Additive	200	200
<i>Enterococcus faecalis</i> ATCC 29212	50	100	0	12.5/3.125	100/25	Synergy	100	<200
<i>Enterobacter cloacae</i> ATCC 13047	50	100	0	50/12.5	100/25	Additive	200	<200
<i>Serratia marcescens</i> ATCC 9986	25	50	0	25/6.25	100/25	Additive	200	200
<i>Aeromonas hydrophila</i> ATCC 35654	50	100	0	25/6.25	50/12.5	Synergy	200	100
<i>Plesiomonas shigelloides</i> ATCC 51903	25	50	0	12.5/3.125	50/12.5	Synergy	200	200
<i>Pseudomonas aeruginosa</i> ATCC 15442	50	100	0	12.5/3.125	100/25	Synergy	200	200
<i>Pseudomonas aeruginosa</i> ATCC 19582	25	100	0	25/6.25	100/25	Additive	200	<200
<i>Acinetobacter calcoaceticus anitratus</i> CSIR	25	100	0	12.5/3.125	25/6.25	Synergy	100	100

4. Discussion

The therapeutic use of antibiotics has been severely compromised by the emergence of drug resistance in many pathogenic bacteria. Hence, polypharmacy, in which drug combinations have been used for treating diseases and reducing sufferings, has been practiced and its use in modern therapeutics has increased. Although this is a common practice, investigating interactions of antibiotics with non-antimicrobial or antimalarial agents becomes essential because of the possible involvement of microbial infections in malaria.

In previous studies, the biochemical and pharmacological effects of antimicrobial agents combined with other drugs [33-36] and those of antimalarials prescribed along with antibiotics for the treatment of infectious diseases as well as their interactions in human have been reported [37,38]. While Khan *et al.* [39] indicated that combining amodiaquine and erythromycin was synergistic in three isolates of *Plasmodium falciparum* but antagonistic in five, Gershon and Howells [40] and Nakornchai and Konthiang [41] reported that interaction of erythromycin and chloroquine was synergistic against chloroquine resistant strain of *P. falciparum* *in vitro*. In *in vivo* assays, Pinichpongse *et al.* [42], Watt *et al.* [43] and Looareesuwan *et al.* [44] indicated that tetracycline combined with quinine and mefloquine against multidrug resistant *P. falciparum* resulted in 83% to 100% cure rate while erythromycin combined with quinine had 80% rapid cure rate against *P. falciparum* [45].

Although *in vitro* studies on the effect of quinine and its interaction with erythromycin on bacteria is scarce, the antibacterial effects of combining erythromycin with quinine against bacteria, in this study, showed that there are interactions between these drugs. Combining erythromycin and quinine resulted in synergistic and additive/indifference interactions more than it being antagonistic. This agreed with Pieren and Tigges [46] who indicated that combination of antibiotics with other compounds not having antimicrobial activity can amplify the effect of an antibiotic. While Clancy and Nguyen [47] reported that combining amphotericin B with azithromycin resulted in synergy against resistant *Fusarium*, Oliver *et al.* [48] reported that the susceptibility of *Candida albicans* was increased when tetracycline was combined with amphotericin B. The additive and synergistic antibacterial effects of the combinations of quinine with erythromycin could, possibly, cause a higher cure rate or a more effective treatment against bacterial infections than would be obtained if erythromycin alone is used. This may be an addition to the current treatment of bacterial infections for which the isolates used have been implicated.

Since macrolides blocks protein synthesis by interacting with the ribosomal subunit [49] to inhibit translocation of peptidyl-tRNA from the receptor to the donor site and the initial steps of 50S subunit assembly [50], erythromycin and its different pro-drugs appear to be less potent inhibitors of drug metabolism [51]. However, while the effect of drug combinations could have resulted from different complex formations within the constituents of the respective drugs, the mechanism of action of the combined drugs could have resulted in complexation of their cationic groups with the phosphate groups of the nucleic acids, cell envelop damage and loss of structural integrity, blockade of RNA synthesis, interference with the cytochrome system and inhibition of oxygen consumption [52], arrest of DNA-dependent RNA synthesis [53], cellular energetic, ribosome binding and protein mistranslation [54] and inhibition of cell wall, DNA, RNA and protein synthesis [55]. The mechanism involved in synergisms could, also, be increased membrane permeability [56] and inhibition of a significant step in peptidoglycan assembly [57]. Thus, the synergistic effect may serve as remedy for urinary tract infection, acute bacterial diarrhea, chronic bronchitis and pneumonia seeing that synergy is a vital part of therapeutic efficacy [58].

5. Conclusion

The previous studies focused on the effects of combining erythromycin and chloroquine/quinine against malaria parasite *in vivo*, this study focused on the effect of combining erythromycin with quinine against bacterial isolates *in vitro*. The antibacterial potential of erythromycin combined with quinine and their synergistic effects are encouraging. However, when erythromycin and quinine are prescribed concurrently in patients with bacterial infections, a close monitoring of the blood concentrations of quinine may be required to avoid supra-therapeutic quinine concentrations that could lead to systemic toxicity. The synergistic and additive/indifference effects, in this study, indicated that combining erythromycin with quinine would be sufficient to treat some bacterial infections if properly managed.

Compliance with ethical standards

Disclosure of conflict of interest

The authors declare that we have no conflict of interest.

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