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DOI: 10.4103/JLP.JLP_170_17

Rosuvastatin as forthcoming antibiotic or as adjuvant additive agent: *In vitro* novel antibacterial study

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Abstract:

INTRODUCTION: Rosuvastatin is a lipid-lowering agent that inhibits 3-hydroxy-3-methylglutaryl coenzyme A reductase leading to a reduction of cholesterol biosynthesis. Many studies have shown an association between statins use and the reduction of sepsis. The aim of the present study was to evaluate the *in vitro* combined antibacterial activity of rosuvastatin and cefixime.

MATERIALS AND METHODS: Five pathogenic bacteria isolates (Gram positive and Gram negative) were used for testing the antibacterial activity of rosuvastatin alone and in combination with cefixime.

RESULTS: Rosuvastatin mainly inhibited *Klebsiella pneumoniae* and *Escherichia coli* where it caused zones of inhibition of $(17.9 \pm 0.6 \text{ mm})$ and $(16.9 \pm 0.3 \text{ mm})$, respectively; however, it moderately inhibited the growth of *Staphylococcus epidermidis* $(12.9 \pm 0.2 \text{ mm})$ and *Staphylococcus aureus* (12.76 ± 0.2) and produced less inhibition for *Pseudomonas aeruginosa* growth where it led to a zone of inhibition equal to $(9.1 \pm 0.5 \text{ mm})$. Minimal inhibitory concentration ($\mu\text{g/mL}$) of rosuvastatin was high compared to cefixime. Fractional inhibitory concentration (FIC) of rosuvastatin was low for *E. coli* and *K. pneumoniae* compared to the other types of bacterial strains. Rosuvastatin exhibited additive effects with cefixime against *E. coli* and *K. pneumoniae*. ΣFIC index was 0.536 and 0.734 for *E. coli* and *K. pneumoniae*, respectively.

CONCLUSION: Rosuvastatin has a significant antibacterial activity against both Gram-negative and Gram-positive bacteria with a potential additive effect when used in combination with cefixime.

Key words:

Antibacterial activity, cefixime, fractional inhibitory concentration, rosuvastatin

Introduction

The increasing phenomenons of bacterial resistance to the antimicrobial agents are due to the improper and indiscriminate use of antimicrobial drugs, which causes drug resistance to become a global health threat. Therefore, the steady increase of bacterial resistance to existing antimicrobial agents is a serious problem; thus, there is a dire need to investigate for new classes of antibacterial agents against infectious diseases.^[1]

Antibiotics exist in large number, but their uses have become limited due to the

development of drug resistance and short- or long-term toxicity. Since the development of a new antibiotic is complicated and difficult, so augmentation of the present antibiotics might be a future clarification.^[2] A number of pharmaceutical preparations and drugs that are used in the management of chronic diseases have shown some antibacterial activity; these agents called nonantibiotics.^[3] Various pharmacological classes have some antimicrobial effects on microbial metabolism; these non-antibiotic agents may have a direct antibacterial activity or augment the effect of antibiotics. Therefore, these nonantibiotics might be adequate to modify bacterial metabolism and act additively or synergistically with some antibiotics.^[4]

How to cite this article: Al-Kuraishy HM, Al-Gareeb AI, Al-Buhadily AK. Rosuvastatin as forthcoming antibiotic or as adjuvant additive agent: *In vitro* novel antibacterial study. J Lab Physicians 2018;10:271-5.

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Submission: 24-11-2017
Accepted: 31-01-2018

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Rosuvastatin is a lipid-lowering agent that inhibits 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase leading to the reduction of cholesterol biosynthesis.^[5] Paricahua *et al.*'s study showed an association between statins use and reduction of sepsis, as atorvastatin can reduce endothelial neutrophil adhesion and cytokine release which reduce the risk of sepsis in patients with peripheral vascular diseases. Moreover, patients on statins are less likely to develop septicemia when becoming infected.^[6] This pleiotropic effect of statins may play a role in the augmentation of specific antibiotic action. Moreover, rosuvastatin has significant antimicrobial effect by unknown mechanism.^[7]

Cefixime is a bactericidal third-generation cephalosporin that inhibits bacterial cell wall synthesis through inhibition of peptidoglycan synthesis, thus it is effective for both Gram-positive and Gram-negative bacteria. Cefixime is used for the treatment of different bacterial infections such as urinary tract infection, gonorrhea, pneumonia, and Lyme disease.^[8]

Drug synergism between known antibiotics and other agents is a novel concept. Therefore, the aim of the present study was to evaluate the *in vitro* combined antibacterial activity of rosuvastatin and cefixime.

Materials and Methods

Bacterial isolates

Five pathogenic bacterial isolates (Gram positive and Gram negative) including *Escherichia coli* (ATCC 25,922), *Klebsiella pneumoniae* (ATCC 100,31), *Staphylococcus epidermidis* (ATCC 12865), *Pseudomonas aeruginosa* (ATCC 195,82), and *Staphylococcus aureus* (ATCC 6538) were obtained from Bacteriology Laboratory/Department of Microbiology/College of Sciences. Bacterial strains were maintained in nutrient agar according to their growth for 24 h at 37°C, and then, one colony from each stock culture was inoculated in 4 mL nutrient broth.

Chemicals

Rosuvastatin 20 mg tablets/once daily (Crestor, AstraZeneca, Plankstadt, Germany) and cefixime tablets USP 400 mg/once daily (Suprax, Lupin Pharmaceuticals, Baltimore, Maryland, USA) were purchased from a private pharmacy. Dimethyl sulfoxide (DMSO) was used as a solvent (DMSO had no antibacterial activity and regarded as a negative control).

Antibacterial activity

The antibacterial activity was evaluated by disc diffusion method that based on the spread of tested agents in a solid medium.^[9] Mueller–Hinton agar was poured in sterile petri dishes (90 mm diameter), and the paper

discs (6 mm diameter) are impregnated with 2 µL rosuvastatin, cefixime, a combination of rosuvastatin with cefixime, and DMSO as a negative control and were placed on the inoculated agar surface. Petri dishes were let to stand for 30 min at room temperature and then at 37°C before incubation for 24 h. The antibacterial effect was reflected by the manifestation of the clear circular zone corresponding to the lack of bacterial growth.

Assessment of minimal inhibitory concentration

Serial dilution method according to the National Committee for Clinical Laboratory Standard^[10] was done to obtain the stock solution of 10 mg of rosuvastatin or 100 mg cefixime which were dissolved in 1 mL DMSO, and then, serial dilutions were prepared. The serially diluted agents were added to plates containing Mueller–Hinton Gold agar and then sterile replicator containing (5×10^5 CFU/drop) of different bacterial strains was placed on each plate. DMSO plate was regarded as control. All plates were incubated for 18 h at 37°C. Minimal inhibitory concentration (MIC) represents the lowest concentration at which no visible growth was detected. Plates were read in duplicate, and then, MICs were recorded regarding breakpoints in tables of the National Committee for Clinical and Laboratory Standards Institute to conclude resistance and susceptibility.

Determination of synergy test

Mueller–Hinton agar plates were inoculated with 0.5 McFarland turbidity standard suspensions of each isolate, and then, the impregnated antibiotic disc alone or in combination with rosuvastatin was placed onto each plate then incubated at 35°C for 48 h for estimation of fractional inhibitory concentration (FIC) index.^[11] For testing of the combination, after application of cefixime for 1 h, it was replaced with rosuvastatin on the same agar. $FIC \text{ of cefixime (A)} = MIC \text{ of drug A in combination} / MIC \text{ of drug A}$, $FIC \text{ of rosuvastatin (B)} = MIC \text{ of drug B in combination} / MIC \text{ of drug B alone}$, then $\Sigma FIC \text{ index} = FIC \text{ of drug A} + FIC \text{ of drug B}$. $\Sigma FIC \text{ index} < 0.5$ indicated synergy, between 0.5 and 1.0 indicated additive effect, between 1.0 and < 4.0 indicated indifference, and above 4.0 indicated antagonism.^[12]

Results

The present study demonstrated a significant antibacterial activity of rosuvastatin against specific bacterial strains. *In vitro* effect of rosuvastatin led to inhibition of bacterial growth that was reflected by the diameter of the zone of inhibition. It mainly inhibited *K. pneumoniae* and *E. coli* where it causes zone of inhibition of (17.9 ± 0.6 mm) and (16.9 ± 0.3 mm), respectively. Rosuvastatin moderately inhibited the growth of *S. epidermidis* (12.9 ± 0.2 mm) and *S. aureus* (12.76 ± 0.2), but it produced less inhibition for

P. aeruginosa where it led to a zone of inhibition equal to (9.1 ± 0.5 mm). Cefixime produced a large zone of inhibition for all of the selected bacterial strains except for *P. aeruginosa*. Combined cefixime and rosuvastatin led to a more significant antibacterial effect than cefixime and rosuvastatin ($P < 0.01$) for all selected bacterial strains [Table 1].

MIC in µg/mL of rosuvastatin was high compared to cefixime mainly for *E. coli* and *K. pneumoniae* ($P < 0.01$). MIC of cefixime was high for *P. aeruginosa* and *S. aureus* and comparatively low for *E. coli* and *K. pneumoniae*. Combination of rosuvastatin and cefixime led to better MIC values primarily against *E. coli*, *K. pneumoniae* and less for other types of bacterial strains compared to cefixime alone [Table 2].

FIC of rosuvastatin was low for *E. coli* and *K. pneumoniae* compared to the other type of bacterial strains. Rosuvastatin exhibited additive effect with cefixime against *E. coli* and *K. pneumoniae*. ΣFIC index was 0.536 and 0.734, respectively, for *E. coli* and *K. pneumoniae* since ΣFIC was between 0.5 and 1.0. Indifference effects were observed for other investigated bacterial strains since ΣFIC was between 1.0 and 4.0 [Table 3].

Discussion

With the raise in the frequency of resistance to antibiotics, alternative agents could be of interest. Some of the nonantibiotic agents are known to have antibacterial effects, which could be of vast magnitude in the treatment of bacterial infections. Various drugs have been estimated not only for direct antibacterial effect but also as resistance-modifying agents through modulation of antibiotic activity or overturning of bacterial resistance.^[13-15]

The present study illustrated significant *in vitro* antibacterial effects of rosuvastatin mainly against *E. coli* and *K. pneumoniae*, as confirmed by Coban *et al.*'s study that confirmed the antibacterial activity of statins.^[16]

The unexpected antibacterial activity of statins was initially observed by Jerwood and Cohen's 2008 study that demonstrated significant antibacterial activity of simvastatin and to a lesser extent fluvastatin against methicillin-resistant *S. aureus* (MRSA) aureus and methicillin-sensitive *S. aureus* (MSSA).^[17]

On the other hand, Graziano *et al.* exemplified that only simvastatin has antibacterial activity against MRSA and MSSA biofilm formation and growth viability.^[18]

Furthermore, many studies showed a significant antibacterial activity of rosuvastatin^[19,20] that correspond with findings of the present study.

Table 1: Zone of inhibition (mm) of cefixime and rosuvastatin

Bacterial isolates	Cefixime	Rosuvastatin	Combination	P
<i>Escherichia coli</i>	19.8±0.5 [§]	16.9±0.3 [§]	20.7±0.9 ^{*§}	0.002*
<i>Klebsiella pneumoniae</i>	20.7±0.6 [§]	17.9±0.6 [§]	21.9±0.6 ^{*§}	0.001*
<i>Staphylococcus epidermidis</i>	12.9±0.8 [§]	12.9±0.2 [§]	17.5±0.6 ^{*§}	0.0001*
<i>Pseudomonas aeruginosa</i>	6.3±0.1 [§]	9.1±0.5 [§]	15.9±0.8 ^{*§}	0.0001*
<i>Staphylococcus aureus</i>	11.8±0.4 [§]	12.76±0.2 [§]	16.2±0.2 ^{*§}	0.0001*

* $P < 0.01$, Tukey HSD *post hoc* test, * $P < 0.01$ (combination vs. rosuvastatin), Tukey HSD *post hoc* test, $P < 0.0001$ compared to the DMSO (negative control). Results are expressed as mean±SE. SE = Standard deviation, DMSO = Dimethyl sulfoxide, HSD = Honestly significant difference

Table 2: Minimal inhibitory concentration (µg/mL) of cefixime and/or rosuvastatin

Bacterial isolates	Cefixime	Rosuvastatin	Combination	P
<i>Escherichia coli</i>	1.3±0.89 [§]	102.88±4.93 [§]	0.7±0.2 [§]	0.0000*
<i>Klebsiella pneumoniae</i>	1.2±0.67 [§]	199.82±3.82 [§]	0.88±0.3 [§]	0.0000*
<i>Staphylococcus epidermidis</i>	66.42±4.97 [§]	201.97±8.49	64.83±4.96 ^{*§}	0.0000*
<i>Pseudomonas aeruginosa</i>	60.45±4.93 [§]	278.78±8.99	60.75±3.81 ^{*§}	0.0000*
<i>Staphylococcus aureus</i>	40.64±3.62 [§]	286.12±7.93	41.55±6.93 ^{*§}	0.0000*

* $P < 0.01$, Tukey HSD *post hoc* test, * $P < 0.01$ (combination vs. rosuvastatin), Tukey HSD *post hoc* Test, $P < 0.01$ compared to the DMSO (negative control). Results are expressed as mean±SE. SE = Standard deviation, DMSO = Dimethyl sulfoxide, HSD = Honestly significant difference

Table 3: Fractional inhibitory concentration of cefixime and/or rosuvastatin

Bacterial isolates	Cefixime	Rosuvastatin	Σ FIC index	Interpretation
<i>Escherichia coli</i>	0.53	0.006	0.536	Additive effect
<i>Klebsiella pneumoniae</i>	0.73	0.004	0.734	Additive effect
<i>Staphylococcus epidermidis</i>	0.97	0.32	1.29	Indifference effect
<i>Pseudomonas aeruginosa</i>	1.0	0.21	1.21	Indifference effect
<i>Staphylococcus aureus</i>	1.02	0.14	1.16	Indifference effect

FIC = Fractional inhibitory concentration

Moreover, the present study demonstrated a significant additive effect of rosuvastatin with cefixime against *E. coli* and *K. pneumoniae*, and indifferent effect against other tested bacterial isolates. It has been theorized that the combination of statins and antibiotics may augment the efficacy of the antibiotic; however, information on the synergistic or additive effect of statins with antibiotics is inadequate and contradictory. Bergman *et al.*'s study confirmed the synergistic activity of simvastatin but not fluvastatin or pravastatin with penicillin against *S. pneumoniae* and *Moraxella catarrhalis*.^[21] In addition,

many studies demonstrated the augmentation of antibiotics effect by statins.^[22,23] Thus, no previous study investigated the antibacterial activity of rosuvastatin in combination with cefixime.

The mechanism of antibacterial activity of statins is uncertain, but it may be through inhibition of mevalonate pathway which is present in both human and Gram-positive bacteria for the synthesis of isoprenoid while Gram-negative bacteria use independent mevalonate pathway for isoprenoid biosynthesis which might explain the sensitivity of Gram-positive bacteria but not Gram-negative bacteria toward statins.^[24] However, in the present study, rosuvastatin mainly inhibited *E. coli* and *K. pneumoniae* regardless of the Gram type as documented by Haeri *et al.*'s study.^[25] Besides, lovastatin did not have any antibacterial activity even on Gram-positive bacteria in spite of potent inhibition of mevalonate pathway; thus, this mechanism is not the main mechanism.^[26]

Moreover, statins attenuate bacterial virulence and production of pro-inflammatory mediators in infected macrophage during acute bacterial infection which minimizes the infection rate,^[27] but in the current study, inflammatory markers were not evaluated.

Rosuvastatin is the synthetic hydrophilic HMG-CoA reductase inhibitor and has a structural similarity with most of the synthetic statins, but unlike other statins, it contains sulfonyl functional group.^[28] This hydrophilic property may limit the penetration of bacterial cell wall mainly in *P. aeruginosa* which might explain the low antibacterial activity of rosuvastatin against *P. aeruginosa*.^[29] In addition, sulfonyl functional group in rosuvastatin may be responsible for the antibacterial effect, since synthetic acylsulfonamides have significant and potent *in vitro* antibacterial effects.^[30]

Further probable mechanism of statins could be due to the inhibition of bacterial biofilm formation through inhibition of bacterial polysaccharide production which is essential for bacterial viability.^[31]

Moreover, quorum sensing (QS) is a vital intercellular communication system in bacteria that play an important role in bacterial pathogenesis.^[32] QS molecule called as acyl-homoserine (AHL) and acts as an agonist for bacterial growth. Rosuvastatin has structural similarity with AHL, thus it interferes with QS system and bacterial motility.^[33]

Herein, further studies are necessary and warranted to illustrate the main mechanism of antibacterial activity of rosuvastatin to ensure safety and efficacy when combined with a specific antibiotic.

Conclusion

Rosuvastatin has significant antibacterial activity against both Gram-negative and Gram-positive bacteria with a potential additive effect when used in combination with cefixime.

Acknowledgments

We would like to acknowledge Dr. Salah Al-windy for his great supports.

Financial support and sponsorship

Nil.

Conflicts of interest

There are no conflicts of interest.

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