Journal of Applied Pharmaceutical Science Vol. 4 (01), pp. 094-100, January, 2014
Available online at http://www.japsonline.com
DOI: 10.7324/JAPS.2014.40116
ISSN 2231-3354

Evaluation of the *in vitro* interaction of amoxicillin and cotrimoxazole antibiotics against resistant bacterial strains

Olufunmiso Olusola Olajuyigbe[1,2*], Olufunke Oyedeji[1] and Otunola Adedayo[1]

[1]Biosciences and Biotechnology Department, Babcock University, Ilisan Remo, Nigeria, [2]Phytomedicine Research Centre, University of Fort Hare, Alice 5700, Eastern Cape, South Africa.

ARTICLE INFO

Article history:
Received on: 06/11/2013
Revised on: 16/12/2013
Accepted on: 09/01/2014
Available online: 30/01/2014

Key words:
Antibacterial combinations, drug-drug interaction, synergy, antibiotics, bacteria.

ABSTRACT

The *in vitro* combination effects of amoxicillin and cotrimoxazole on clinical isolates was investigated using the agar diffusion and macrobroth dilution methods. The results showed that these organisms had varied susceptibility to the different concentrations of each of these antibiotics and their combinations. The susceptibility of the isolates to the antibacterial combinations showed that they were susceptible in the following order: *Streptococcus pyogenes* (TD2) > *Streptococcus pyogenes* (TD10) > *Streptococcus pneumoniae* (TE10) > *Salmonella typhi* (TC6) > *Salmonella typhi* (TC2). The macrobroth assay showed a drastic reduction in the minimum inhibitory concentrations of both antibiotics. While the MIC of amoxicillin ranged between 0.1202 and 0.4808 µg/ml and that of cotrimoxazole ranged between 0.2405 and 0.9619 µg/ml, the MIC of the antibacterial combinations ranged between 0.00305 and 0.0150 µg/ml. A statistical analysis of the zones of inhibitions produced by the antibiotics and their combinations indicated that the mean differences between the zones of inhibitions were significantly diverse. This study showed that there was synergistic interaction between amoxicillin and cotrimoxazole *in vitro* and could be an alternative choice of therapy for the treatment of streptococcal and gastrointestinal infections in which these organisms have been implicated.

INTRODUCTION

Hospital patients frequently receive more than one antibacterial agent and these agents may interact with each other and with other drugs (Jankel and Speedie, 1990). A drug interaction refers to a change in the magnitude or duration of the pharmacological response of one drug because of the presence of a second drug (Brodey *et al.,* 1998). Drug interactions may result from changes in the pharmacodynamic and pharmacokinetics properties of the drug. While pharmacodynamic drug interactions are relatively common in practice and adverse effects can usually be minimized if interactions are anticipated and appropriate counter measures are taken (Katzung, 2001), combination of drugs may be used to minimize the development of resistant strains, instigate a synergistic effect and reduce toxicity (Tortora *et al.*, 1989). Similarly, these combinations of different drugs are used in empiric therapies to cover a wide spectrum of potential pathogens when the causative agent is unidentified or when infection is likely to be due to mixture of organisms (Andreoli *et al.*, 1997). Combinations of drugs can be additive when both drug acts independently, synergistic when the effect of the two drugs given together is significantly greater than the sum of the individual effect of the two drugs acting separately or antagonistic if the drugs become less effective than when taken alone (Bhatia and Ichhpujani, 2004). Previously, different interactions between amoxicillin and other drugs have been reported. Adam *et al*. (1983) reported that the combination of amoxicillin and flucloxacillin was synergistic against beta-lactamase-producing organisms. Cuffini *et al*. (1998) showed that amoxicillin/clavulanic acid had excellent synergistic antimicrobial activities against *Streptococcus pneumoniae*. Proton pump inhibitors such as esomeprazole and rabeprazole combined with amoxicillin showed synergistic activity in eradicating *Helicobacter pylori* (Go, 2002). Although amoxicillin do not affect theophilline clearance (Jonkman, 1986) and antagonism of gentamicin and amoxicillin against *Escherichia coli* and *Enterobacter cloacae* strains was reported by Grzybowska *et al.,* (2004), Dogterom *et al*. (2005) showed that there are no pharmacokinetic interactions between etonogestrol and ethinylestradiol combined with amoxicillin while combining doxycycline and amoxicillin may reduce the effectiveness of amoxicillin (http, 2013).

* *Corresponding Author*
E-mail: funmijuyigbe12@yahoo.com; Tel: +234-8101994655,

On account of having successful therapies, polypharmacy has become the usual practice when a patient report in a hospital. However, because of the development of resistance to antibiotics, co-administrations of antibiotics are encouraged as this could result in effective therapeutic outcomes. Since resistance to amoxicillin and cotrimoxazole by many bacteria have been widely reported, this study was designed to investigate the *in vitro* combination effects of these antibiotics against clinical isolates of *Streptococcus pneumoniae*, *Streptococcus pyogenes* and *Salmonella typhi.*

MATERIALS AND METHODS

Bacteria used and inoculum preparation

The bacteria used in this study included *Salmonella typhi* (TC2), *Salmonella typhi* (TC6), *Streptococcus pyogenes* (TD2) *Streptococcus pyogenes* (TD10), and *Streptococcus pneumoniae* (TE10) which are clinical strains obtained from Lagos State University Teaching Hospitals, Lagos State, Nigeria. They were identified and confirmed using morphological, microscopy and biochemical tests following standard procedures described by Cowan and Steel (1974) and Cheesbrough (2006).

Drug Preparations

Pure powders of amoxicillin and cotrimoxazole were used. Stock antibiotic solutions were prepared and dilutions made according to the CLSI (Clinical Laboratory Standardization Institute) method or manufacturer's recommendations (NCCLS, 1997; Richard, 2007).

Here, 0.0197 g of Trimethoprim and 0.0985 g of Sulfamethoxazole were combined in the ratio 1:5 as cotrimoxazole. This mixture was dissolved in 10 ml of absolute acetone while 0.0985 g of amoxicillin was dissolved in 10 ml of sterile distilled water to form their (w/v) stock solution. Different concentrations (15.38, 30.78, 61.56, 123.12, 246.3, and 492.5 µg/ml) of both antibiotics were prepared and used during this study while the stock solutions were stored in a freezer at -20^{o}C until use.

Agar Diffusion Susceptibility Testing with Cotrimoxazole and Amoxicillin

Each of the isolates was standardized using colony suspension method. Each strain's suspension was matched with 0.5 McFarland standards to give a resultant concentration of 1.5×10^8 cfu/ml. The antibiotic susceptibility testing was determined using the modified Kirby–Bauer diffusion technique (Cheesbrough, 1987) by swabbing the Mueller-Hinton agar (MHA) (Oxoids UK) plates with the resultant saline suspension of each strain. Wells were then bored into the agar medium with heat sterilized 6 mm cork borer.

The wells were filled with 100 µL of different concentrations prepared for the amoxicillin alone, cotrimoxazole alone and their combinations taking care not to allow spillage of the solutions onto the surface of the agar. The plates were allowed to stand for at least 1 h before being incubated at 37°C for 24 h (BSAC, 2002). The determinations were done in duplicate. After 24 h of incubation, the plates were examined for zones of inhibition (Bauer *et al.,* 1966). The diameter of the zones of inhibition produced by the amoxicillin alone, cotrimoxazole alone and their combinations were measured and interpreted using the CLSI zone diameter interpretative standards (CLSI, 2008).

Determination of MIC by Broth Dilution Methods

The minimum inhibitory concentrations (MICs) for the amoxicillin alone, cotrimoxazole alone and their combinations were determined in duplicate by the macrobroth dilution method in Mueller-Hinton broth according to CLSI (Clinical Laboratory Standardization Institute) (Richard, 2007). Different concentrations of each of the antibiotic and their combinations ranging from 1.202 to 2462.5 µg/ml were prepared. One millilitre (1 ml) of each working antibiotic concentration was serially diluted in Mueller Hinton broth.

After the serial dilution, 100 µl of each of the adjusted bacterial strains was dispensed into each tube containing each antibiotic or their combinations and incubated at 37^{o}C for 24 h. The minimum inhibitory concentration (MIC) was expressed as the lowest concentrations which inhibited growth as judged by the lack of turbidity in the tube. As a control, a tube containing antibiotic alone and a tube containing inoculums alone, in each rack, was incubated simultaneously along with other tubes containing inoculums for MIC determination. The MIC was defined as the lowest dilution that showed no growth in the Mueller Hinton broth.

Determination of Minimum Bactericidal Concentration (MBC)

The MBC was determined by sampling all the macroscopically clear tubes and the first turbid tube in the series. Before being sampled, the tubes were gently mixed by flushing them with a sterile pipette before being subcultured on nutrient agar and incubated at 37^{o}C overnight. . After the incubation periods, the lowest concentrations of the antibacterial agents that did not produce any bacterial growth on the solid medium were regarded as their MBC values (Irkin and Korukluoglu, 2007). This observation was matched with the MIC test tube that did not show evidence of growth after 48 h of incubation.

Statistical analysis

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 zones of inhibition obtained from the different concentrations of the extract tested against the microorganisms. All statistical analyses were done using SAS software (1999) model.

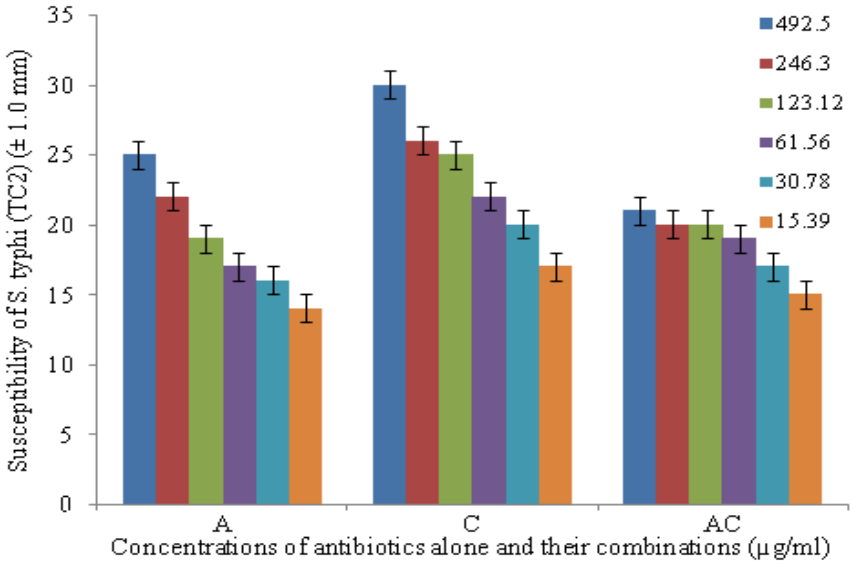

Fig. 1: *In vitro* susceptibility of *Salmonella typhi* (TC2) (Mean ± Std. dev) to Amoxicillin alone (A), Cotrimoxazole alone (C) and their combinations (AC).

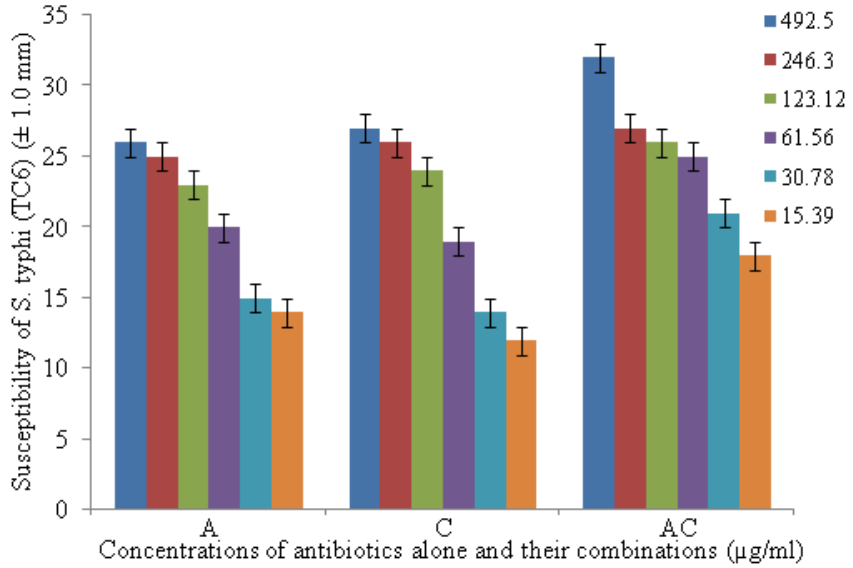

Fig. 2: *In vitro* susceptibility of *Salmonella typhi* (TC6) (Mean ± St. dev) to Amoxicillin alone (A), Cotrimoxazole alone (C) and their combinations (AC).

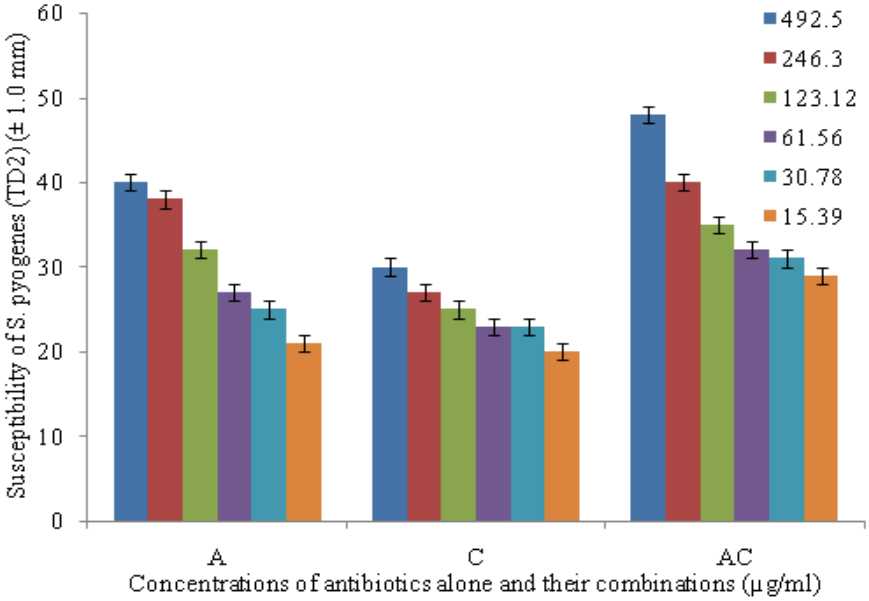

Fig. 3: *In vitro* susceptibility of *Streptococcus pyogenes* (TD2) (Mean ± St. dev) to Amoxicillin alone (A), Cotrimoxazole alone (C) and their combinations (AC).

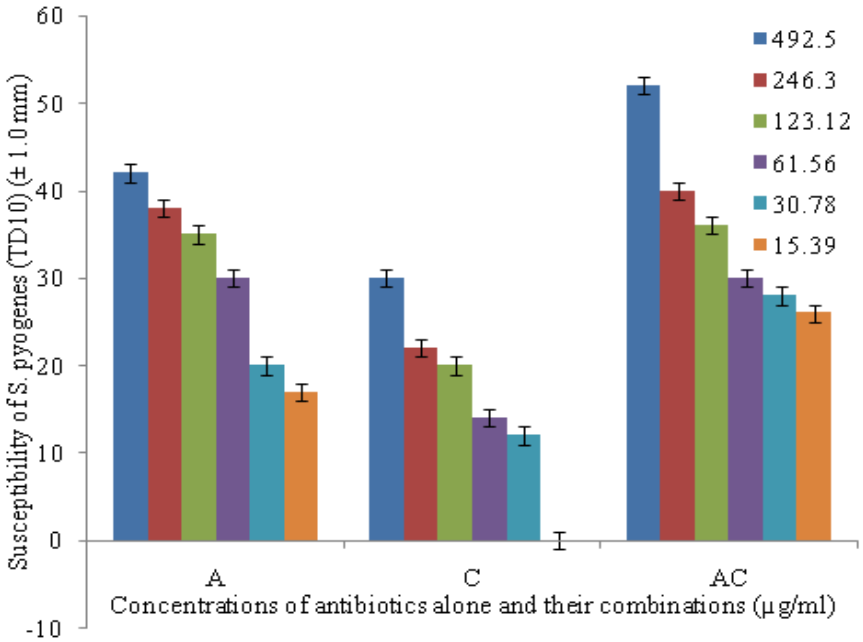

Fig. 4: *In vitro* susceptibility of *Streptococcus pyogenes* (TD10) (Mean ± Std. dev) to Amoxicillin alone, Cotrimoxazole alone and their combinations.

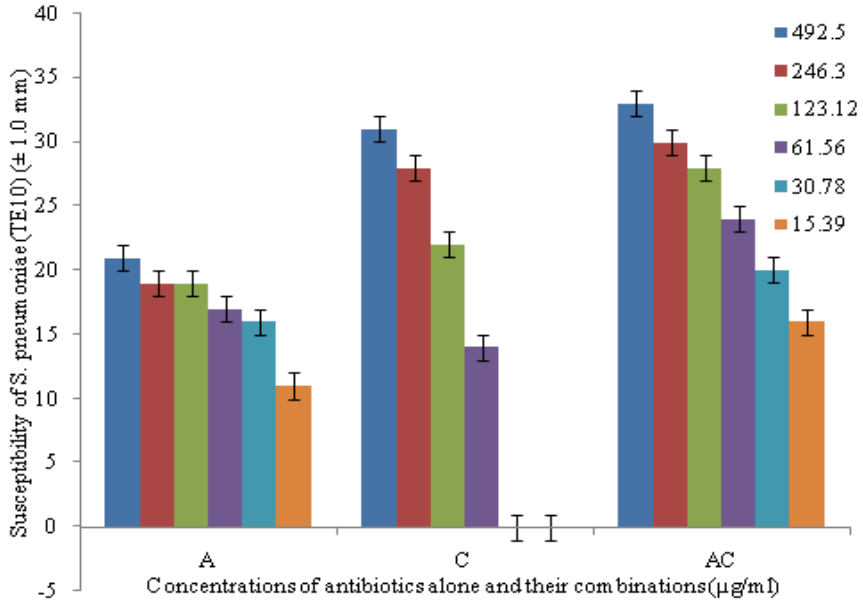

Fig. 5: *In vitro* susceptibility of *Streptococcus pneumoniae* (TE10) (Mean ± St. dev) to Amoxicillin alone (A), Cotrimoxazole alone (C) and their combinations (AC).

Table 1: *In vitro* effects of amoxicillin, cotrimoxazole and their combinations against the test isolates

	MIC range	MBC range
	----------(µg/ml)----------	
Amoxicillin	0.1202 - 0.4808	0.0241 - 0.0962
Cotrimoxazole	0.2405 - 0.9619	0.4804 - 1.924
Cotrimoxazole + Amoxicillin	0.0035 - 0.0150	0.0035 - 0.0301

Table. 2: Mean differences ± Standard Errors in the antibacterial effects of amoxicillin, cotrimoxazole and their combinations against the test isolates.

		***Salmonella typhi* (TC2)**	***Salmonella typhi* (TC6)**	***Streptococcus pyogenes* (TD2)**	***Streptococcus pyogenes* (TD10)**	***Streptococcus pyogenes* (TD2)**
Antibiotic concentrations and their combinations (µg/ml)		Mean Difference ± Std. Error	Mean Difference ± Std. Error	Mean Difference ± Std. Error	Mean Difference ± Std. Error	Mean Difference ± Std. Error
	Cot (492.5)	-5.00 ± 0.41	-1.00(*) ± 0.082	10.00(*) ± 0.082	12.00(*) ± 0.080	-10.00(*) ± 0.078
	Amox + Cot (492.5 + 492.5)	4.00(*) ± 0.41	-6.00(*) ± 0.082	-18.00(*) ± 0.082	-12.00 (*) ± 0.080	-12.00(*) ± 0.078
	Amx (246.3)	3.00(*) ± 0.41	1.00(*) ± 0.082	2.00(*) ± 0.082	4.00(*) ± 0.080	2.00(*) ± 0.078
	Cot (246.)	-1.00(*) ± 0.41	0.00(*) ± 0.082	13.00(*) ± 0.082	20.00(*) ± 0.080	-7.00(*) ± 0.078
	Amox + Cot (246.3+ 246.3)	5.00(*) ± 0.41	-1.00(*) ± 0.082	0.00 ± 0.082	2.00(*) ± 0.080	-9.00(*) ± 0.078
	Amx (123.12)	6.00(*) ± 0.41	3.00(*) ± 0.082	8.00(*) ± 0.082	7.00(*) ± 0.080	2.00(*) ± 0.078
	Cot (123.12)	0.00(*) ± 0.41	2.00(*) ± 0.082	15.00(*) ± 0.082	22.00(*) ± 0.080	-1.00(*) ± 0.078
	Amox + Cot (123.12+ 123.12)	5.00(*) ± 0.41	0.00 ± 0.082	5.00(*) ± 0.082	6.00(*) ± 0.080	-7.00(*) ± 0.078
Amx (492.5)	Amx (61.56)	8.00(*) ± 0.41	6.00(*) ± 0.082	13.00(*) ± 0.082	10.00(*) ± 0.080	4.00(*) ± 0.078
	Cot (61.56)	3.00(*) ± 0.41	7.00(*) ± 0.082	17.00(*) ± 0.082	28.00(*) ± 0.080	7.00(*) ± 0.078
	Amox + Cot (61.56+61.56)	6.00(*) ± 0.41	1.00(*) ± 0.082	8.00(*) ± 0.082	12.00(*) ± 0.080	-3.00(*) ± 0.078
	Amx (30.78)	9.00(*) ± 0.41	11.00(*) ± 0.082	15.00(*) ± 0.082	22.00(*) ± 0.080	5.00(*) ± 0.078
	Cot (30.78)	5.00(*) ± 0.41	12.00(*) ± 0.082	17.00(*) ± 0.082	30.00(*) ± 0.080	21.00(*) ± 0.078
	Amox + Cot (30.78+ 30.78)	8.00(*) ± 0.41	4.00(*) ± 0.082	9.00(*) ± 0.082	14.00(*) ± 0.080	1.00(*) ± 0.078
	Amx (15.39)	11.00(*) ± 0.41	12.00(*) ± 0.082	19.00(*) ± 0.082	25.00(*) ± 0.080	10.00(*) ± 0.078
	Cot (15.39)	8.00(*) ± 0.41	14.00(*) ± 0.082	20.00(*) ± 0.082	42.00(*) ± 0.080	21.00(*) ± 0.078
	Amox + Cot (15.39+15.39)	10.00(*) ± 0.41	8.00(*)± 0.082	11.00(*) ± 0.082	16.00(*) ± 0.080	5.00(*) ± 0.078

Key: Amx = amoxicillin; Cot = cotrimoxazole; * = significant difference ($p < 0.05$)

RESULTS

The effects of antibacterial activities of amoxicillin alone, cotrimoxazole alone and their combinations at different concentrations were investigated against clinical isolates of *Salmonella typhi* (TC2), *Salmonella typhi* (TC6), *Streptococcus pyogenes* (TD2) *Streptococcus pyogenes* (TD10), and *Streptococcus pneumoniae* (TE10). In this study, the susceptibility of these isolates was concentration dependent. Cotrimoxazole was more effective against the two strains of *Salmonella typhi* (TC2 and TC6) than amoxicillin. While the antibacterial combination showed synergy against *Salmonella typhi* (TC6), antagonistic effect was observed in *Salmonella typhi* (TC2) although the combination effects at lower concentrations ranging between 15.39 and 123.12 µg/ml showed synergy and indicated higher antibacterial effect than what was obtained in amoxicillin. In the *S. pyogenes* strains (TD2 and TD10), amoxicillin exhibited higher antibacterial effects than cotrimoxazole. Their combinations indicated synergy when compare with the antibacterial effects of cotrimoxazole and amoxicillin alone against the two strains of *S. pyogenes*. In *S. pneumoniae* (TE10), cotrimoxazole was more effective at concentrations ranging between 61.56 and 492.5 µg/ml than amoxicillin. Comparatively, the combination of the two antibiotics was consistently synergistic.

A comparative analysis of the susceptibility of these isolates to amoxicillin alone showed that TD10 was the most susceptible, followed by TD2 > TC6 > TC2 > TE10. The susceptibility of the isolates to the cotrimoxazole showed that TD2 was the most susceptible, followed by TC2 > TC6 > TD10 > TE10. The susceptibility of the isolates to the antibacterial combinations showed that they were susceptible in the following order: TD2 > TD10 > TE10 > TC6 > TC2. Although these organisms had varied susceptibility to the different concentrations of each of these antibiotics and their combinations, the antibacterial combinations showed synergistic interactions that were dependent on the susceptibility of each of the isolates (Table 1 – 5). The macrobroth assay of the interaction between the two antibiotics showed a drastic reduction in the minimum inhibitory concentrations of both antibiotics. While the MIC of amoxicillin ranged between 0.1202 and 0.4808 µg/ml and that of cotrimoxazole ranged between 0.2405 and 0.9619 µg/ml, the MIC of the antibacterial combination ranged between 0.00305 and 0.0150 µg/ml (Table 1). A statistical analysis of the zones of inhibitions produced by different concentrations of amoxicillin, cotrimoxazole and their combinations indicated that the mean difference between the zones of inhibitions were significantly different as shown in Tables 2. A $p < 0.05$ was considered significant.

DISCUSSION

A number of therapeutic agents with different structures and mechanisms of action have been combined and implicated in drug-drug interactions (Yamreudeewong *et al.*, 2003; Niami *et al.*, 2003; Zou *et al.*, 2005). Many drugs used in combination with antibiotics have shown different interactions of clinical significance. While clinically important interactions occur occasionally, most drug combinations do not result in significant adverse interactions and interactions severe enough to warrant reducing dosages are rare (Greenblatt, 2001). Although the incidence of clinically important adverse drug interactions remain unknown (Bianco, 1992) and adverse effects of drug interactions account for only a small fraction of all adverse effects (Fuhr, 2000), several drug combinations have resulted in positive interactions, negative interactions and interactions in which neither of the drugs had any effects on each other *in vivo* when the

bioavailability of each drug combined was considered. However, to increase the antimicrobial spectrum of these drugs (Chait *et al.,* 2007), antibiotic combinations could be used in combating the dramatic increase in the number of bacteria pathogens which are resistant to conventional antibiotics (Service, 1995; Davies, 1996). Although there is dearth of information on the interactions between amoxicillin and cotrimoxazole, interactions of amoxicillin and other therapeutic agents had been reported (Darras-Jolly *et al.,* 1996; Chan *et al.,* 2007; Olajuyigbe, 2012). Since the antibacterial combination of antibiotics has gained interest because it often resulted in a synergistic antibacterial effect enabling the dose of the individual drugs to be reduced (Barriere, 1992), this study gave credence to synergistic interactions that would be able to prevent the development of drug-resistance (Wu *et al.,* 1999**;** Steenbergen *et al.,* 2009) to amoxicillin and cotrimoxazole *in vitro*. In agreement with Lorian (1991) who showed that the bactericidal activity could best be achieved by the combination of two different antibiotics rather than the effect produced by an individual antibiotic, the mechanism of synergistic action that resulted in high bactericidal effect may involve the penetration of amoxicillin into the peptidoglycan layer to prevent of cross-links, inhibit cell wall synthesis and, therefore, increase the permeability of the different bacterial strains to cotrimoxazole that acts sequentially in preventing folic acid synthesis (Kutty *et al.,* 1998). The synergistic effect may, also, be due to the formation of certain complexes which became more effective in inhibiting these clinical isolates either by inhibiting the cell synthesis or by causing its lyses or death.

In conclusion, the steady increase in bacterial resistance to existing drugs is a serious problem. As resistance to old antibiotics spreads, there is a dire need to search for new classes of antibacterial substances if the problem is to be contained. Consequently, investigating newer drugs to which there is lesser resistance and combining old antibiotics for synergistic interactions against clinical bacterial pathogens becomes essential in an era where high toxicity are associated with newer antibacterial agents and funding for discovery of new therapeutic agent has been retracted. Since the need of the moment is to develop newer, useful and important antimicrobial agents capable of overcoming bacterial resistance, the resultant synergy in the combination of amoxicillin and cotrimoxazole is a novel concept as such combinations will have different mechanism of action which may lead to new choices of therapeutic agents for the treatment of streptococcal and gastrointestinal infections in which these organisms have been implicated. These combinations can enhance the efficacy of amoxicillin and cotrimoxazole and could be used effectively in treating respiratory infections as well as gastrointestinal infections caused by multidrug resistant microorganisms having no effective therapy available.

REFERENCES

Adam D, Koeppe P, Heilmann HD. Pharmacokinetics of amocixillin and flucloxacillin following the simultaneous intravenous administration of 4g and 1g, respectively. Infection, 1983; 11(3):150-4.

Andreoli TE, Bennett JC, Charles CJ, Plum FC. 1997. CECIL ESSENTIALS OF MEDICINE. 'Infectious Diseases. 4th edition. W. B. Saunders Company, Philadelphia. pp 660.

Barriere SL. Bacterial resistance to beta-lactams, and its prevention with combination antimicrobial therapy. Pharmacother, 1992; 12:397-402.

Bauer AW, Kirby WM, Sherris JC, Truck M. Antibiotic susceptibility testing by a standardized single disk method. Am J Clin Pathol, 1966; 45:493–496.

Bhatia R, Ichhpujani RL. 2004. Essentials of Medicine. 3rd edition. Jaypee Brothers Medical Publishers Limited, New Delhi. Pp 61.

Bianco TM. Drug interactions. Clin Ped Med Surg, 1992; 9(2): 223-38.

Brodey TM, Lamer J, Minneman KP. 1998. Human Pharmacology: Molecular to Clinical. 'Issues in Therapeutics'. 4thed. Mosby. pp 77.

BSAC, Author. Disc diffusion method for antimicrobial susceptibility testing. Br Soc Antimicrob Chemother, 2002, (2. 1. 2):1–46.

Chait R, Craney A, Kishony R. Antibiotic interactions that select against resistance. Nature, 2007; 446(7136):668-71.

Chan YY, Ong YM, Chua KL. Synergistic Interaction between Phenothiazines and Antimicrobial Agents against *Burkholderia pseudomallei.* Antimicrob Agents Chemother, 2007, 51(2):623–630.

Cheesbrough M. 2006. Medical Laboratory Manual for Tropical Countries, II Micrbiology (ELBS), Butterworth, Kent, U.K. pp. 23-78.

Cheesbrough M. 1987.Medical Laboratory Manual for Tropical Countries, 2th ed.; Butterworth-Heinemann: Cambridge, UK.

Clinical and Laboratory Standard Institute (CLSI). 2008. Performance Standards for Antimicrobial Susceptibility Testing Eighteenth Informational Supplement, M100-S18; CLSI: Wayne, PA, USA.

Cowan SJ, Steel KJ. 1974. Cowan and Steel manual for identification of medical bacteria, 2nd edn Cambridge University Press, London, pp. 176-232.

Cuffini AM, Tullio V, Ianni Palarchio, A, Bonino A, Paizis G, Carlone NA. Enhanced effects of amoxycillin/clavulanic acid compared with amoxycillin and clavulanic acid alone on the susceptibility to immunodefenses of a penicillin resistant strain of *Streptococcus pneumoniae*. Drugs Exp Clin Res, 1998; 24(4):173-84.

Darras-Joly C, Bedos JP, Sauve C, Moine P, Vallee E, Carbon C, Carbon C, Azoulay-Dupuis E, Synergy between amoxicillin and gentamycin in combination against a highly penicillin-resistant and tolerant strain of *Streptococcus pneumoniae* in a mouse pneumonia model. Antimicrob Agents Chemother, 1996; 40:2147-51.

Davies J. Bacteria on the rampage. Nature 1996; 383:219–220.

Dogterom P, van den Heuvel MW, Thomsen T. Absence of pharmacokinetic interactions of the combined contraceptive vaginal ring NuvaRing with oral amoxicillin or doxycycline in two randomised trials. Clin Pharmacokinet, 2005, 44(4):429-38.

Fuhr, U. "Clinically significant" new drug interactions. Med. Klin. 2000; 95(1 Spec No):18-22.

Go MF. Treatment and management of *Helicobacter pylori* infection. Curr Gastroenterol Rep, 2002; 4(6):471-7.

Greenblatt DJ. 2001. Adsorption interactions to improve bioavailability. Program and abstracts of the 41st Interscience Conference on Antimicrobial Agents and Chemotherapy; Chicago, Illinois. Presentation 1279.

Grzybowska W, Banaszczyk-Ruś M, Tyski S. Interaction of aminoglycosides and the other antibiotic on selected bacterial strains. Med Dosw Mikrobiol. 2004; 56(3):275-85.

Http, 2013. Drug interactions between amoxicillin and Doxy-Caps. http://www.drugs.com/drug-interactions/amoxicillin-with-doxy-caps-187-0-940-2651.html (Accessed 11th March, 2013)

Irkin R, Korukluoglu M. Control of *Aspergillus niger* with garlic, onion and leek extracts. Afr J Biotechnol, 2007; 6(4):384–387.

Jankel CA, Spedie SM. Detecting drug interactions: a review of the literature. DICP, 1990; 24(10):982-9.

Jonkman JH. Therapeutic consequences of drug interactions with theophylline pharmacokinetics. J Allergy Clin Immunol, 1986; 78(4 Pt 2):736-42.

Katzung GB. 2001. Basic and Clinical Pharmaology. 'Important drug interactions and their mechanism. 8th edition. Pp 1122-1123.

Kutty K. Berg DD, Sebastian JL, Kochar MS, Meviis BA. 1998. Kochar's Concise Textbook of Medicine. 2nd Edition. Williams and Williams, pp. 612 - 614.

Lorian V. 1999. Antibiotics in laboratory medicine. Williams & Wilkins (Baltimore) 3rd ed., pp. 1248.

National Committee for Clinical Laboratory Standards (NCCLS). 1997. Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically, 4th ed.; Approved Standard M7-A4; NCCLS: Wayne, PA, USA.

Niami M, Backman JT, Fromm MF, Neuvonen PJ, Kivisto KT. Pharmacokinetic interactions with rifampicin: clinical relevance. Clin Pharmacokinetics, 2003; 42(9):819-850

Olajuyigbe OO. Synergistic influence of tetracycline on the antibacterial activities of amoxicillin against resistant bacteria, J Pharm Allied Health Sci, 2012; 2(1):12-20.

Richard S, Lynn SM, Avery CG. 2007. Antimicrobial Susceptibility Testing Protocols; CRC Press: New York, NY, USA.

SAS, Proprietary software release 8.2. SAS institute Inc. NC., USA.

Service RF, Antibiotics that resist resistance. Science, 1995; 270:724–727.

Steenbergen JN, Mohr JF, Thorne GM. Effects of daptomycin in combination with other antimicrobial agents: A review of *in vitro* and animal model studies. J Antimicrob Chemother, 2009; 64:1130–1138.

Tortora GT, Funke BR, Case CL. 1989. MICROBIOLOGY: An Introduction. 3rd edition. Benjamin/Cummings Publishing Incorporation. Pp 12

Wu YL, Scott EM, Po AL, Tariq VN. Ability of azlocillin and tobramycin in combination to delay or prevent resistance development in *Pseudomonas aeruginosa*. J Antimicrob Chemother, 1999; 44:389–392.

Yamreudeewong W., M. L. G. DeBisschop, G. Martin and D. L. Lower. 2003. Potentially significant drug interactions of class III antiarrhythmic drugs. Drug Saf, 1999; 26(6):421-438.

Zou S, Chan E, Duan W, Huang M, Chen YZ. Drug bioactivation, covalent binding to target proteins and toxicity relevance. Drug Metab Rev, 2005; 37(1):41-213.

How to cite this article:

Olufunmiso Olusola Olajuyigbe, Olufunke Oyedeji and Otunola Adedayo. Evaluation of the *in vitro* interaction of amoxicillin and cotrimoxazole antibiotics against resistant bacterial strains. J App Pharm Sci, 2014; 4 (01): 094-100.