DRUG ANTIBIOTIC INTERACTIONS-ANTIMALARIALS

Pages with reference to book, From 37 To 40

Najma Sultana (Department of Pharmaceutical Chemistry, University of Karachi, Karachi-32.)
M. Saeed Arayne (Department of Chemistry, University of Karachi, Karachi-32.)

Abstract

The antimicrobial effects of four antimalarials were determined. The effect of the chosen drugs when combined with a selected number of antibiotics was studied on Staphylococcus aureus and Escherichia coli to determine the types of interaction. Most antimalarials showed either no effect or a synergistic action. However, some exhibited antagonistic effects, which may be either due to some physical interaction or some unselective blockade of certain receptor sites essential to the action of antibiotics. (JPMA 36: 37, 1986).

INTRODUCTION

The term “drug interactions” has probably been used for about two decades. Yet it certainly is not a new occurrence. The simultaneous use of two or more drugs must have been practiced since ancient times. Polypharmacy is not a modem phenomenon although its extent in modern therapeutics may be increasing[1]. The bioavailability of drugs at theft site of action can be enhanced or reduced by interaction with other drugs. Several studies concerning the biochemical and pharmacological effects of antimicrobial agents when given with other drugs are reported in the literature.[2-6] The type of interactions reported involve competition for renal tubular excretion, displacement from carrier sites, chelation, decreased protein synthesis, increased tissue toxicity, acid.base neutralization and many others[1,5-7]

Antimalarials are generally prescribed along with antibiotics for the treatment of infectious diseases. The pharmacological and biochemical actions of these drugs as well as their interactions in humans have been studied throughly[8-11]

However, few ‘in vitro’ studies on the effect of these drugs and their interaction with antibiotics on microorganisms have been reported. The antimicrobial effect of quinine and quinacrine was subject of several studies and these drugs proved to be syneçgistic with antibiotics by preventing the emergence of resistant microorganisms.[12-14] Their mechanism of action included complexation of the cationic groups of such drugs with the phosphate groups of nucleic acids, alteration or lysis of the cell wall, alteration of cell permeability, inhibition of spore germination, blockade of RNA synthesis, interference with the cytochrome system and inhibition of oxygen consumption.

In this investigation, it was of interest to determine the antimicrobial activity of certain antimalarials generally prescribed with antibiotics in the treatment of infectious diseases when tested alone and in combination with antibiotics. The type of interaction are also reported.

EXPERIMENTAL

Stock Cultures and Test Organisms:

Cultures of Escherichia coil, Proteus vulgaris, Salmonella typhi, Pseudomonas aeruginosa, Staphylococcus aureus, Streptococcus pyogenes, Bacillus subtilis and Candida albicans were maintained on slants of dextrose nutrient agar (Difco) or blood agar and stored at 4°C. Subculturing was carried out every 2 weeks.

Determination of Minimum Inhibitory Concentrations (MIC) of Drugs with Antibiotics:
A stock solution was prepared to contain 4 mg/ml of the thug or 1 mg/mi of antibiotic. Compounds that were insoluble in water were first dissolved in small quantities of either 95% ethanol or 50% dimethyl sulfoxide and then the solutions were diluted to volume with sterile distilled water or 1% phosphate buffer, pH6-8[15,16]
Twofold serial dilutions of the stock solutions were carried out in nutrient broth except with Str. pyogenes where dilution was carried out in brain heart infusion; the diluted solutions were distributed in S ml quantities in test tube. Each test tube was inoculated with 0.1 ml of the suspension of the test organism (1-2 x 106 cells/mI). The inoculated media were incubated at 37°C for 18 24 hr. and the MIC was then recorded. Each experiment was performed in triplicate.

Procedure for Interaction Study:

Nine test tubes each containing 3 ml of dextrose nutrient broth (1 .66X), were diluted to 5 ml by adding I ml each of the antibiotic and drug solution. The final concentration of the drug and the antibiotic in the tubes in tenns of the MIC are shown in Table 1.

Table I
Concentration of Drugs and Antibiotics in Different Tubes.

Drug	one-fourth MIC	one-half MIC	MIC
one–fourth MIC	1	2	3
one–half MIC	4	5	6
MIC	7	8	9

As a general practice for drugs that did not show antimicrobial activity, 100 pg/mi was used instead of the MIC. Each test tube was then inoculated with a 0.1 ml of the suspension of the test organism and incubated for 18-24 hr. Each experiment was performed in triplicate.
A positive control for growth and a negative control for the MIC of both the drug and the antibiotic were carried out concurrently with each experiment.
The interaction between the drug and the antibiotic were recorded as synergistic (5) when the bacteriostatic action was manifested in tubes 1,2 and 4 (Table 1) and antagonistic (A) when growth was produced in tubes 3 and 5-9.

Spectrophotometrie Studies:

When solutions of antimalarials and the antibiotics separately and in combination, at different mole ratios, were scanned in the UV region, no evidence of interaction could be observed in the resulting spectra.

RESULTS AND DISCUSSION

The activities of the tested drugs on different microorganisms are given in Table II.

Table II
MIC of Antimalarials against Different Microorganisms.

DRUGS	E. coli	P. vulgaris	S. typhi	Ps. aeruginosa	Staph. aureus	Str. pyogenes	B. subtilis	C. albicans
Quinine dihydrochloride	N	500	500	1000	N	125	1000	N
Chloroquine diphosphate	N	N	1000	N	N	500	N	N
Primaquine diphosphate	1000	N	25	N	1000	63	1000	1000
Quinacrine	500	N	125	N	1000	16	N	1000

N = No effect at 1000 μg of drug/ml.

All the antimalarials investigated had moderate antimicrobial activity. Among the tested gram positive microorganisms, Str. pyogenes were relatively less responsive against all the antimalarials except chloroquine diphosphate which had no effect on any other gram positive micro-organism. Similarly quinine dthydrochloride and chloroquine diphosphate were inactive against Staph. aureus and C. albicans while chloroquine diphosphate and quinacrine were inactive against B. subtiis. Primaquine diphosphate and Quinacrine were most responsive against Staph. aureus and C. albicans.
Among the gram negative microorganisms tested, all the drugs were irresponsive except. quinine dihydrochloride against P. vulgaris and Ps. aeruginosa. Quinine dthydrochloride and Chloroquine diphosphate were inactive against E. coli, but were most responsive against Ps. aeruginosa and S. typhi respectively, while Primaquine diphosphate and quinacrine being most responsive against E. coli but the later being less responsive than against gram positive microorganisms.
Synergism and antagonism between different antimicrobial agents have been studied using various methods. [17,18] To study the interactions of the drugs with antibiotics, it was necessary to determine the MIC of the antibiotics against two strains of Staph aureus and E. coli. The types of interactions between the different antimalarials and antibiotics are shown in table III Quinine dihydrochioride was antagonistic with streptomycin sulphate, and dihydrostreptomycin sulphate, while chioroquine diphosphate was antagonistic with penicillin G and penicillin v. However, both showed a synergistic effect with chiorotetracycline hydrochloride. On the other hand, the other antimalarials quinacrine and primaquine were synergistic with most of the tested antibiotics (Table III).

Table III
Interaction between Antimalarials with Antibiotics as shown by Their Effect on Staph. aureus and E. Coli.*

Antibiotics	Quinine dihydrochloride		Chloroquine diphosphate		Primaquine diphosphate		Quinacrine	
	Staph. aureus	E. coli	Staph. aureus	E. coli	Staph. aureus	E. coli	Staph. aureus	E. coli
Erythromycin	–	–	–	–	S	S	S	S
Streptomycin sulfate	A	A	–	–	S	S	S	S
Dihydrostreptomycin sulfate	A	A	–	–	S	S	S	S
Chloramphenicol	–	–	–	–	S	S	S	S
Penicillin G. Sodium	–	–	A	–	S	S	S	S
Penicillin V. Potassium	–	–	A	–	S	S	S	S
Ampicillin Sodium	–	–	–	–	S	S	S	S
Tetracycline Hydrochloride	–	–	–	–	S	–	S	S
Oxytetracycline hydrochloride	–	–	–	–	S	S	S	S
Chlorotetracycline	S	S	S	S	S	S	S	S
Methacycline hydrochloride	–	–	–	S	S	S	S	S
Kanamycin sulphate	–	–	–	–	–	S	–	S

*= A = antagonistic, S= synergistic. The dash (––) indicates that the results were found as expected; either no growth occurred (the total concentration was equal to MIC or more) or growth occurred (the total concentration was less than the MIC).

The antagonistic effects observed with quinine dihydrochioride in combination with Streptomycin and dthydrostreptomycin might be explained on the basis that this drug could unselectively block certain receptor sites essential to the action of antibiotics. Since Spectrophotometric measurements of mixtures of antibiotics that the results were found as expected; either no growth or growth occurred (the total concentration was less than the and antimalarials excluded chemical interaction, there must be another site of activity of the antimalarials in the bacterial cell.

Further studies on the mechanism of action of drugs showing synergistic and antagonistic effects are in progress. In conclusion, this type of interactions may have clinical implications and it seems that the indiscriminate administration of drug-antibiotic combination is questionable and may not be advisable because such ‘in vitro’ interactions may occur ‘in vivo.

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