IN VITRO ACTIVITY OF SOME NEWER QUINOLONE COMPOUNDS

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SYNOPSIS

The quinolones are a group of antimicrobial agents that act by inhibiting bacterial DNA gyrases, enzymes essential in DNA replication. Several newer quinolone agents have been introduced recently. These are broad spectrum agents which may be administered orally. In-vitro susceptibility testing of five quinolone agents namely norfloxacin, pefloxacin, enoxacin, ofloxacin and ciprofloxacin against recent clinical bacterial isolates at the General Hospital Kuala Lumpur was performed. The results confirm the broad spectrum and high activity of these agents against these isolates which included Pseudomonas aeruginosa and methicillin-resistant Staphylococcus aureus. The quinolones would provide valuable alternatives in the treatment of infections caused by organisms resistant to the more commonly used antibiotics.

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INTRODUCTION

The quinolones are synthetic compounds which are related to nalidixic acid (1). They are heterocyclic carbon acids and act by inhibiting bacterial DNA gyrases. The DNA gyrases are essential for DNA replication. Recently several new quinolone compounds have been introduced. These compounds have a wide spectrum of activity which includes Pseudomonas aeruginosa. Their activity against anaerobic bacteria and streptococci is however rather poor. The newer quinolones are well absorbed from the gastrointestinal tract thus making oral administration feasible. Their low serum protein binding and small molecular sizes enable them to penetrate extravascular sites extremely well therefore achieving therapeutic concentrations in many tissues. These antimicrobial agents are therefore potentially very useful drugs in the treatment of infections. The purpose of this study is to establish their in-vitro effectiveness against recent clinical isolates at the Kuala Lumpur General Hospital.

METHODS

A total of 369 isolates of both Gram positive and Gram negative organisms were obtained from clinical specimens of patients at the Kuala Lumpur General Hospital. They comprised 45 strains of E. coli, 45 strains of Enterobacter sp., 46 strains of Proteus sp., 40 strains of Acinetobacter calcoaceticus var anitratus, 48 strains of Salmonella sp. (including 7 strains of Salmonella typhi), 47 strains of Klebsiella sp., 50 strains of Pseudomonas aeruginosa and 48 strains of Staphylococcus aureus of which 19 were methicillin-resistant.

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Pure powders of the quinolone compounds to be tested were obtained from their respective manufacturers. They were norfloxacin (Astra), enoxacin (Warner-Lambert), pefloxacin (May and Baker), ofloxacin (Dai-Ichi) and ciprofloxacin (Bayer). The minimal inhibitory concentrations (MIC) of these quinolones against the clinical isolates were determined using a standard agar plate dilution method. The medium used was Diagnostic Sensitivity Test agar (Oxoid) which contained doubling dilutions of the quinolone compounds ranging from 0.007 to 32.0 mg/L. Approximately 10^5 colony forming units of each organism were inoculated onto the plates using a Denley multiple inoculator. The plates were incubated at 37°C for 18 hours. The minimum inhibitory concentration was taken as the lowest concentration of the compound that inhibited all growth.

RESULTS

Table 1 summarises the results of the susceptibility testing. The results are expressed as MIC_{50} and MIC_{90} which are the concentrations of the compound that inhibits 50% and 90% of the organisms tested respectively. All five quinolone compounds were highly active against the Enterobacteriaceae with values of MIC_{90} ranging from 0.03 to 4.0 mg/L. Enoxacin and norfloxacin were found to be less active against Acinetobacter calcoaceticus var anitratus with MIC_{90}s of 16.0 mg/L. Against Pseudomonas aeruginosa enoxacin was the least active compound (MIC_{90} of 8.0 mg/L). All the quinolone compounds were found to be effective against both methicillin sensitive and methicillin-resistant Staphylococcus aureus. On an activity by weight basis, ciprofloxacin was found to be the most active compound and exoxacin the least with norfloxacin, pefloxacin and ofloxacin in between.

DISCUSSION

The results obtained were generally similar to those published in other studies (2)(3) although our values for enoxacin MICs tend to be a little higher. Enterobacteriaceae were very sensitive and the majority of strains were inhibited by concentrations of quinolones below 1 mg/L.

Acinetobacter calcoaceticus var anitratus strains were rather less susceptible, particularly with enoxacin and norfloxacin. Ofloxacin appears to be the most active among the five quinolones against Acinetobacter calcoaceticus var anitratus. MICs against Pseudomonas aeruginosa were generally higher. The activity of enoxacin against Pseudomonas aeruginosa strains was rather disappointing (MIC_{50}) = 4.0 mg/l and MC_{90} = 8.0 mg/l). Ciprofloxacin was found to be the most active compound against Pseudomonas aeruginosa. The quinolones were also found to be active against both methicillin-resistant and methicillin sensitive Staphylococcus aureus.

Antibiotic resistance is a major problem in our hospital (4). In a recent survey, 21% of Enterobacteriaceae strains and 36% of Pseudomonas aeruginosa strains isolated in our hospital were found to be resistant to gentamicin. Nearly 20% of Staphylococcus aureus strains were resistant to both methicillin and gentamicin. In such cases quinolones may be useful alternatives provided there are no contraindications to their use. Ciprofloxacin would be the quinolone of choice in Pseudomonas aeruginosa infections.

Although resistance to quinolones among local clinical isolates appear to be uncommon at the moment, resistance can emerge during therapy. Resistance to quinolones primarily arises through mutation (5) but a plasmid carrying resistance to nalidixic acid has also been reported recently (6). Both clinician and microbiologist should therefore monitor closely the emergence of such resistance.

Quinolones are also known to cause adverse effects (7). Perhaps the most serious potential side effect is the destruction of growing cartilage. Thus, its use in children is contraindicated. Nausea and dermatitis have also been reported and administration of pefloxacin to dogs in high doses can produce cataracts.

We have shown that the newer quinolones have useful in-vitro activity against local clinical isolates. However careful clinical trials will have to be conducted to establish its clinical usefulness in the local situation.

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Table 1
THE ACTIVITY OF 5 QUINOLONES AGAINST CLINICAL ISOLATES

Organism (number of isolates) and antibotic	MIC(mg/l) range	MIC_{50}	MIC_{90}
E. coli (45)			
Pefloxacin	<0.007-0.03	0.125	0.125
Ofloxacin	0.015-0.125	0.06	0.06
Enoxacin	0.06-0.5	0.25	0.5
Ciprofloxacin	<0.007-0.03	<0.007	0.015
Norfloxacin	0.03-0.125	0.06	0.125
Enterobacter sp (45)			
Pefloxacin	0.06-1.0	0.125	0.5
Ofloxacin	0.03-1.0	0.06	0.125
Enoxacin	0.5-4.0	0.5	2.0
Ciprofloxacin	0.015-0.5	0.03	0.125
Norfloxacin	0.03-1.0	0.06	0.25
Proteus sp (46)			
Pefloxacin	0.06-1.0	0.125	0.5
Ofloxacin	0.03-0.5	0.125	0.25
Enoxacin	0.25-4.0	1.0	2.0
Ciprofloxacin	<0.007-0.5	0.03	0.125
Norfloxacin	0.03-2.0	0.06	0.5
Salmonella sp (48)			
Pefloxacin	0.06-0.5	0.25	0.25
Ofloxacin	0.03-0.5	0.125	0.125
Enoxacin	0.5-1.0	0.5	1.0
Ciprofloxacin	<0.007-0.25	0.015	0.03
Norfloxacin	0.06-1.0	0.12	0.25
Klebsiella sp (47)			
Pefloxacin	0.06-2.0	0.25	0.5
Ofloxacin	0.03-2.0	0.125	0.25
Enoxacin	0.12-8.0	0.5	4.0
Ciprofloxacin	0.007-0.5	0.03	0.25
Norfloxacin	0.06-2.0	0.125	2.0
Acinetobacter sp (40)			
Pefloxacin	0.06-2.0	0.5	1.0
Ofloxacin	<0.007-1.0	0.25	0.5
Enoxacin	0.25-32	4.0	16.0
Ciprofloxacin	<0.007-2.0	0.25	2.0
Norfloxacin	0.06-16.0	4.0	16.0
Pseudomonas aeruginosa (50)			
Pefloxacin	1.0-8.0	2.0	4.0
Ofloxacin	0.5-4.0	1.0	2.0
Enoxacin	2.0-8.0	4.0	8.0
Ciprofloxacin	0.06-1.0	0.25	0.5
Norfloxacin	0.25-8.0	1.0	2.0
Methicillin resistant S. aureus (19)			
Pefloxacin	—	0.25	0.25
Ofloxacin	0.12-0.25	0.12	0.25
Enoxacin	—	4.0	4.0
Ciprofloxacin	0.25-1.0	0.5	1.0
Norfloxacin	0.5-4.0	2.0	4.0
Methicillin sensitive S. aureus (29)			
Pefloxacin	0.25-0.5	0.25	0.5
Ofloxacin	—	0.25	0.25
Enoxacin	—	4.0	4.0
Ciprofloxacin	0.25-1.0	0.5	1.0
Norfloxacin	1.0-4.0	2.0	4.0

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