In Vitro Activities of Cloxyquin (5-Chloroquinolin-8-ol) against Mycobacterium tuberculosisV

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The in vitro activities of cloxyquin (5-chloroquinolin-8-ol) against 9 standard strains and 150 clinical isolates of Mycobacterium tuberculosis were studied. The MICs ranged from 0.062 to 0.25 μg/ml. The MIC50 and MIC90 were 0.125 and 0.25 μg/ml, respectively. These indicate that cloxyquin exhibited good antituberculosis activity, even for multidrug-resistant isolates.

Current first-line drugs for treatment of tuberculosis consist of only 5 agents, i.e., isoniazid (INH), rifampin (RIF), ethambutol (EMB), pyrazinamide (PZA), and streptomycin (STR). Resistance to the first-line drugs, especially RIF and INH, usually causes treatment failure and necessitates the use of the second-line drugs with a prolonged period of therapy. Even with that, treatment frequently fails. New antituberculous agents, especially the ones with novel mechanisms of action are urgently required.

Bihalogenated 8-hydroxyquinolines (quinolin-8-ols) are a group of known drugs with antiamebic activities and were widely used to treat intestinal infection. The commonly used ones include broxyquinoline, clioquinol chlorquinaldol, and iodoquinol (4, 6). They also exhibit antibacterial and antifungal activities (1, 14).

Herewith, we report the antituberculosis activities of a monohalogenated 8-hydroxyquinoline, cloxyquin (5-chloroquinolin-8-ol), against 150 clinical Mycobacterium tuberculosis isolates, including multidrug-resistant strains. Cloxyquin (Fig. 1) was known to possess activities against bacteria, fungi, and protozoa (3, 10, 11, 12), but the antimycobacterial activity has never been documented.

A total of 159 strains of M. tuberculosis, including 9 reference strains (H37Rv ATCC 27294, H37Ra ATCC 25177, H37Rv-PAS-R ATCC 35821 [p-aminosalicylic acid resistant], H37Rv-CS-R ATCC 35826 [cycloserine resistant], H37Rv-KM-R ATCC 35827 [kanamycin resistant], H37Rv-PZA-R ATCC 35828 [pyrazinamide resistant], H37Rv-TAC-R ATCC 35829 [thiacetazone resistant], H37Rv-ETA-R ATCC 35830 [ethionamide resistant], and H37Rv-EMB-R ATCC 35837 [ethambutol resistant]) and 150 isolates from pulmonary and extrapulmonary patients in Ramathibodi Hospital, Bangkok, Thailand, including 100 sensitive strains, 20 drug-resistant strains (7, 3, 3, and 12 isolates resistant to INH, RIF, EMB, and STR, respectively), and 30 multidrug-resistant (MDR) strains (7 isolates resistant to INH and RIF, 3 isolates addi-

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FIG. 1. Chemical structure of cloxyquin.
0.125 to 0.25 μg/ml. Similarly, the MICs of cloxyquin for 150 clinical isolates ranged from 0.062 to 0.25 μg/ml. The MIC\textsubscript{50} and MIC\textsubscript{90} were 0.125 and 0.25 μg/ml, respectively (Table 1). There were no statistically significant differences of MICs between drug-sensitive, drug-resistant, and MDR strains. Nor were there any observable differences in MICs of strains with different antibiotic resistance patterns. The MICs of RIF and INH against \textit{M. tuberculosis} H37Rv were 0.031 and 0.062 μg/ml, respectively.

The fact that cloxyquin is equally active across various mono- and multidrug-resistant clinical isolates suggested that its mechanism of action is not shared by previously known drugs. The antimicrobial action of bihalogenated 8-hydroxyquinolines is likely to relate to their chelating activities. It is proposed that the iron chelation deprives the microbes of the essential nutrient. However, the mechanisms may actually be more complex. For example, bihalogenated 8-hydroxyquinolines were found to inhibit the RNA-dependent DNA polymerase of respiratory syncytial virus by chelation of copper (17) and to inhibit RNA synthesis by chelation of Mn\textsuperscript{2+}, Mg\textsuperscript{2+}, and Zn\textsuperscript{2+} (9). Moreover, the antibacterial action may be the property of the metal complexes but not the free compounds (13, 17). It had previously been proposed that iodinated 8-hydroxyquinolines are effective against \textit{Mycobacterium tuberculosis} and \textit{Mycobacterium avium}. It was found to inhibit the RNA-dependent DNA polymerase of 

\begin{table}
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\begin{tabular}{|c|c|c|c|}
\hline
\textit{M. tuberculosis} strain type (n) & No. (%) of isolates for which MIC (μg/ml) is: & \\
\hline
& 0.062 & 0.125 & 0.25 \\
\hline
Drug sensitive (100) & 15 (15) & 74 (74) & 11 (11) 0.25 \\
Drug resistant (20) & 2 (10) & 13 (65) & 5 (25) 0.25 \\
MDR (30) & 5 (16.7) & 24 (80) & 1 (3.3) 0.125 \\
Total (150) & 22 (14.7) & 111 (74) & 17 (11.3) 0.25 \\
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\end{tabular}

* MIC\textsubscript{50} are 0.125 μg/ml for all groups.*
\end{table}

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\textbf{REFERENCES}


