Ofloxacin Susceptibilities of 5,667 Neisseria gonorrhoeae Strains Isolated in Hong Kong

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Ofloxacin is a new quinolone that has potent in vitro antibacterial activity against both gram-positive and gram-negative organisms (14). Studies in developed countries (1–3, 7, 8, 10, 12) have documented the efficacy of ofloxacin in the treatment of uncomplicated gonorrhea as well as nongonococcal urethritis, while the feasibility of using ofloxacin in the treatment of urethritis in developing areas has occasionally been reported (4, 12, 13). In Hong Kong, ofloxacin has been used in Government Social Hygiene (sexually transmitted disease) Clinics as first-line empirical treatment for urethritis since 1985 in single doses of 400 and 600 mg for males and females, respectively. We have previously published our results (11) on the changes in the penicillin susceptibility of Neisseria gonorrhoeae since the introduction of ofloxacin. In the study described here, we studied the changes in the susceptibility of this organism to ofloxacin over a 3-year period.

Population studied and data collected. The Government Social Hygiene Clinics mainly serve lower- to middle-social-class populations and are scattered over most urban districts within the Hong Kong territory. A total of 5,667 strains of N. gonorrhoeae isolated from patients attending the Social Hygiene Clinics between 1 January 1990 and 31 December 1992 were tested for their susceptibilities to ofloxacin.

Antibiotic susceptibility study. The collected specimens were immediately inoculated onto modified Thayer-Martin medium supplemented with 1% IsoVitaleX (Oxoid, Basingstoke, England)–antibiotic supplement LCAT (Oxoid)–5% horse blood. After incubation at 35°C in 5% CO2 for 48 h, all strains were identified by colony morphology, Gram staining, the oxidase test, and production of acid from glucose but not maltose, lactose, or sucrose in Cystine Trypticase agar (BBL, Cockeysville, Md.).

The agar dilution method (16) was used to determine the breakpoint susceptibilities to ofloxacin for all strains. Briefly, the medium used was GC agar base (Oxoid) containing 1% Vitox (Oxoid) and hemoglobin. The concentrations used were 0.01, 0.1, and 1 µg/ml. These were chosen because an initial study showed that for our strains, the MIC for 50% of isolates tested is 0.01 µg/ml and the MIC for 90% of isolates tested is 0.1 µg/ml, and strains for which the MIC is ≥2 µg/ml would fall outside the susceptible range (15) and would indicate probable clinical failure. The inoculum was grown overnight on horse blood agar supplemented with 1% Vitox, suspended in saline, and adjusted to 107 CFU/ml. The bacterial suspension was inoculated onto antibiotic-containing medium by using a multipoint inoculator (Mast, Merseyside, England) which delivered 0.001 ml per spot, resulting in a final inoculum of 104 CFU per spot. After overnight incubation at 35°C in 5% CO2, the endpoint was read as the lowest concentration of drug giving complete growth inhibition.

Control strains of N. gonorrhoeae (CDC F-18 [ATCC 49226], CDC F-28, and CDC F-45) and Staphylococcus aureus NCTC 6571, Escherichia coli NCTC 10418, and Pseudomonas aeruginosa NCTC 10662 were included in all susceptibility tests. The MICs of ofloxacin remained in the acceptable range for these control strains throughout the study.

A total of 5,667 strains of N. gonorrhoeae were studied (Table 1). The number of positive isolates per month varied from 114 to 218 (standard deviation, 26.4). This number remained stable, and there was no decrease in this trend, as we had recorded in previous years (11). Before March 1992, 0.01 µg of ofloxacin per ml consistently inhibited about 50% of strains. Thereafter, a steady increase in the percentage of strains that grew at that concentration was seen, with more than 90% of strains growing in ofloxacin at that concentration in the last 3 months of 1992. On the other hand, the percentage of strains growing at 0.1 µg/ml (MIC, ≥0.1 µg/ml) showed an earlier and almost linear rise from about 5% in February 1990 to 50% in December 1992. A similar change was also observed when the 0.25-µg/ml concentration was monitored; the proportion of strains that grew at that concentration rose from 10.1% in August 1992 to 35.8% in December 1992. No significant increase was seen for those growing at 1 µg/ml (MIC, ≥2 µg/ml); this was also reflected in the lack of clinical failures during this period. The preliminary data for 1993 appear to confirm the trend of decreasing susceptibility.

Although clinical failures have been reported for ciprofloxacin (9), another quinolone widely used in European countries, recent studies show that gonococci remain exclusively susceptible to ofloxacin, despite its extensive use in the Southeast Asian region (4, 5, 6, 13). In the present study, we documented the fact that while ofloxacin has been used as first-line treatment for urethritis, a decrease in susceptibility was observed only after 5 years, as indicated by the breakpoint concentrations chosen. It could be argued that a
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full determination of the MICs for all strains might have been able to detect a change even earlier.

Thus, 0.1 \( \mu \text{g/mL} \) seems to be the earliest indicator for the gradual upward shift in the MIC for the population studied. The most probable explanation for the present trend of decreasing susceptibility is antibiotic selection pressure on susceptible mutants, although the exact mechanism remains to be elucidated. While the decreased susceptibility observed may be due to the spread of a single clone, our preliminary observations (7a) with monoclonal serotyping suggest that multiple clones, including a number of transient and resident strains in the local population, are involved. Since about 60% of our strains are locally acquired (11), the rest come from neighboring countries including the People's Republic of China, Macau, Thailand, and the Republic of Korea. It would be particularly interesting if the same trends were seen in those areas.

Another question is at what MIC will clinical failures become significant. At present, even with 30% of strains growing at 0.25 \( \mu \text{g/mL} \) (i.e., MIC, \( \geq 0.5 \mu \text{g/mL} \)), there is still no sign of significant clinical failures. Although the MIC breakpoint for ofloxacin is usually twofold higher than that for ciprofloxacin, we think that it is unlikely that the 0.008- \( \mu \text{g/mL} \) ciprofloxacin breakpoint that has been suggested (9) can be directly translated into a 0.016- \( \mu \text{g/mL} \) breakpoint for ofloxacin. Close monitoring is warranted, because the emergence of quinolone resistance could severely compromise the usefulness of quinolones in the treatment of sexually transmitted diseases in this region. Furthermore, the 2- \( \mu \text{g/mL} \) breakpoint for other gram-negative organisms may or may not need to be modified for gonococci.

REFERENCES


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