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Susceptibility of *Nocardia asteroides* to New Quinolones and β-Lactams

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The susceptibility of 31 strains of *Nocardia asteroides* to various quinolones and beta-lactams, as well as coumermycin, amikacin, and minocycline, was determined by the agar dilution technique. Ciprofloxacin was the most active fluoroquinolone tested on a weight basis, as it inhibited approximately 50% of the isolates at achievable drug levels in serum. Ceftriaxone and cefpirome were the most active cephalosporins in this system with MICs of 8 μg/ml for 80% of strains tested. Imipenem, amikacin, and minocycline were the most effective agents tested.

Nocardia asteroides is a pathogen in the immunologically incompetent and immunologically normal host (4, 15). Depending upon the site infection and the immunological status of the patient, this disease can be associated with extremely high mortality rates (14).

Sulfonamides are the preferred therapy for many forms of nocardiosis, yet there are reports of patients unsuccessfully treated with these agents (5). There are also patients who develop side effects, necessitating the withdrawal of these compounds. Other antimicrobial agents, such as amikacin and imipenem, as well as several newer beta-lactams, have shown activity against *N. asteroides* in vitro, as well as in an experimental model of cerebral nocardiosis (6, 7, 9, 10). There are also reports of successful therapy with agents other than the sulfa compounds (3).

A class of carboxyquinolones is being tested in a wide range of clinical settings, and these agents have been shown to have an extremely broad spectrum of activity against a variety of organisms, particularly the family *Enterobacteriaceae* (1, 11, 16). These agents are inhibitors of DNA gyrase and are not subject to alteration or degradation by plasmid-mediated mechanisms. The present study was designed to determine if members of the carboxyquinolones, as well as several other antimicrobial agents, have in vitro activity against *N. asteroides*.

The in vitro susceptibility of 31 strains of *N. asteroides* to six quinolones, six cephalosporins, and other antimicrobial agents, was determined by the agar dilution technique. These strains were obtained from patients with a variety of forms of nocardial infections. All strains were identified by standard criteria.

A loopful of each isolate was placed in 50 ml of brain heart infusion broth and incubated in a rotary incubator. After 48 h, 1 ml of a homogeneous solution of *N. asteroides* was subcultured into another 50 ml of brain heart infusion broth. The organisms were in a homogeneous suspension, and little visible or microscopic clumping was observed. These cultures were incubated for 72 h in a rotary incubator as described above. After this period of incubation, all flasks were turbid and the suspensions were homogeneous. Colony counts were assayed, and each culture contained between 10^7 and 10^9 CFU of *N. asteroides* per ml of broth. These suspensions were placed into the wells of a Steers replicator, which delivered 0.002 ml per inoculum spot onto agar plates. These agar plates contained serial twofold dilutions of antibiotics, with concentrations ranging from 64 to 0.03 μg/ml. The MIC was defined as the lowest antibiotic concentration suppressing all growth at 48 h of incubation at 37°C.

The antibiotics used in this study and their sources were: cinoxacin, Eli Lilly & Co., Indianapolis, Ind.; enoxacin, Warner-Lambert Co., Ann Arbor, Mich.; ofloxacin, Ortho Pharmaceutical Corp., Raritan, N.J.; amifloxacin and WIN 35439, Sterling Drug, Inc., Rensselaer, N.Y.; ciprofloxacin, Miles Pharmaceuticals, West Haven, Conn.; ceftriaxone and coumermycin, Hoffman-La Roche Inc., Nutley, N.J.; ceftazidime and cefuroxime, Glaxo Pharmaceuticals, Inc., Research Triangle Park, N.C.; ceftizoxime, Smith Kline & French Laboratories, Philadelphia, Pa.; cefmenoxime, Abbott Laboratories, North Chicago, Ill.; cefpirome, Hoechst-Roussel Pharmaceuticals Inc., Somerville, N.J.; aztreonam, E. R. Squibb & Sons, Princeton, N.J.; ticarcillin-clavulanic acid (Timentin) and amoxicillin-clavulanic acid (Augmentin), Beecham Laboratories, Bristol, Tenn.; apalcillin, Wyeth Laboratories, Inc., Philadelphia, Pa.; amikacin, Bristol Laboratories, Syracuse, N.Y.; and imipenem, Merck Sharp & Dohme, Rahway, N.J.

The activity of the antimicrobial agents used in this study against 31 strains of *N. asteroides* is shown in Table 1. The carboxyquinolones used in this study generally had poor activity against our isolates. On a weight basis, ciprofloxacin was the most active quinolone, yet only 50% of the strains were inhibited by achievable drug concentrations in serum. The same was true for ofloxacin but at higher concentrations. These two agents differ in their peak concentrations in serum and other pharmacokinetic properties which may make them therapeutically equivalent (16; personal communication, William J. Novick, Jr., data on file, Hoechst-Roussel Pharmaceuticals, Inc.). The broad-spectrum cephalosporins showed variable activity against these isolates. Ceftriaxone and cefpirome had similar activity, as approximately 80% of the strains were inhibited by achievable drug concentrations in serum (13). This is similar to the activity shown by cefotaxime as reported previously (7). Aztreonam was inactive against these strains. Of the clavulanate antibiotics, only amoxicillin-clavulanic acid showed moderate activity, as it inhibited 50% of the isolates at ≤16 μg/ml. Coumermycin had activity similar to that of amoxicillin-clavulanic acid. Minocycline, amikacin, and imipenem were

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TABLE 1. Comparative activities of antimicrobial agents against 31 strains of *N. asteroides*

Antibiotic	MIC (μg/ml)[a]		
	Range	50%	90%
Cinoxacin	8–>64	>64	≥64
Enoxacin	2–64	32	64
Ofloxacin	0.125–>64	8	64
Amifloxacin	0.5–>64	64	>64
WIN 35439	0.5–64	16	64
Ciprofloxacin	0.125–32	4	8
Ceftizoxime	0.25–>64	32	>64
Ceftazidime	8–>64	64	>64
Ceftriaxone[b]	0.25–>64	4	>64
Cefmenoxime	4–>64	>64	>64
Cefpirome[b]	0.06–>64	1	64
Cefuroxime	4–>64	32	>64
Aztreonam	>64	>64	>64
Amoxicillin-clavulanic acid	0.5–>64	16	32
Ticarcillin-clavulanic acid	0.25–>128	>128	>128
Apalcillin	4–>64	32	>64
Minocycline	0.06–2	2	2
Coumermycin	0.06–>64	8	>64
Amikacin	0.125–32	1	8
Imipenem	≤0.06–8	2	4

[a] 50% and 90%, MICs for 50 and 90% of the isolates, respectively.
[b] MIC for 80% of the isolates was 8 μg/ml.

the most active antibiotics against *N. asteroides*, which is in agreement with previous findings. These agents inhibited all isolates at concentrations below achievable peak drug levels in serum.

There have been recent reports on the susceptibility of *N. asteroides* to newer antimicrobial agents alone and in combination (6–8, 10). Studies have been necessary as a result of the failure of standard sulfonamide treatment in some patients and the intolerance to this type of therapy in others (3, 5). Despite successful treatment in some patients, sulfa compounds do not appear to be bactericidal against many strains of *N. asteroides*. This lack of bactericidal activity may in part account for high mortality rates in the immunologically incompetent patient with certain forms of nocardiosis. This may also be the reason for the prolonged therapy needed to eradicate or continually suppress this organism. In the experimental model, there are other treatments based on susceptibility studies which proved to be superior to the sulfa compounds (9). They are, specifically, amikacin and imipenem.

Early reports showed a lack of correlation between in vitro susceptibility and in vivo clinical efficacy (2, 12). Some recent data show otherwise, as there are several antimicrobial agents with demonstrable in vitro activity that have proven efficacy in an experimental model. The data presented herein suggest that none of the very broad-spectrum carboxyquinolones has good activity against a broad range of *Nocardia* isolates, that cetriaxone and cefpirome are active against the majority of these strains at achievable drug levels in serum, and that, in agreement with previous reports, imipenem, minocycline, and amikacin have the lowest MICs in this test system. Further in vitro testing with newly developed agents against *N. asteroides* is warranted, as the mortality rates for this infection remain high. Also, these tests may lead the clinician to choose the most appropriate treatment for the individual patient. The data may also help in determining what antibiotics would be promising for testing in an experimental model of intracerebral and possibly other forms of nocardiosis.

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