Susceptibility of community Gram-negative urinary tract isolates to mecillinam and other oral agents

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OBJECTIVE: To determine the susceptibility of community outpatient Gram-negative urinary tract isolates to mecillinam and other commonly used oral agents.
DESIGN AND SETTING: The study was a laboratory-based study of consecutive Gram-negative urinary tract isolates. Only those isolates considered to be significant pathogens were included in the study. Susceptibility testing was performed using agar dilution methodology following guidelines published by the National Committee for Clinical Laboratory Standards.
POPULATION STUDIED: Outpatients presenting to a family physician or clinic with signs or symptoms suggestive of a urinary tract infection were included in the study.
MAIN RESULTS: Of 2000 consecutive community isolates (91.8% *Escherichia coli*, 3.9% *Klebsiella* species, 2.0% *Proteus* species, 2.3% others), in vitro susceptibilities were: mecillinam 98.8%, ampicillin 77.0%, ciprofloxacin 100%, trimethoprim/sulfamethoxazole 91.6% and nitrofurantoin 95.4%. Susceptibility to mecillinam was significantly better than all other agents except ciprofloxacin ($P<0.001$, McNemar's test). Organisms with reduced susceptibility to mecillinam included *Citrobacter* species, *Pseudomonas aeruginosa* and *Providencia* species.
CONCLUSIONS: Community Gram-negative urinary tract isolates remain highly sensitive to mecillinam and ciprofloxacin, but a significant number have developed resistance to trimethoprim/sulfamethoxazole. Further studies are required to determine the clinical significance of these results.

Key Words: *Gram-negative organisms; Outpatients; Urinary tract infections*

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La sensibilité des isolats des voies urinaires à Gram négatif au mécillinam et autres agents oraux dans la communauté

OBJECTIF : Déterminer la sensibilité des isolats des voies urinaires à Gram négatif au mécillinam et autres agents oraux dans la communauté.
MODÈLE ET CONTEXTE : L'étude menée en laboratoire portait sur des isolats des voies urinaires à Gram négatif consécutifs. Seuls les isolats considérés comme des agents pathogènes importants ont été retenus dans l'étude. Les tests de sensibilité ont été menés en utilisant la technique de dilution en gélose, suivant les lignes directrices publiées par le *National Committee for Clinical Laboratory Standards*.
POPULATION ÉTUDIÉE : L'étude a été menée auprès de malades externes consultant un médecin de famille ou une clinique et manifestant des signes ou symptômes d'infection des voies urinaires.
PRINCIPAUX RÉSULTATS : Sur 2000 isolats de malades externes consécutifs (91,8 % d'*Escherichia Coli*, 3,9 % du genre *Klebsiella*, 2,0 % du genre *Proteus*, autres 2,3 %), les sensibilités *in vitro* ont été de : mécillinam, 98,8 % ; ampicilline, 77,0 % ; ciprofloxacine, 100 % ; triméthoprime-sulfaméthoxazole, 91,6 % ; et nitrofurantoïne, 95,4 %. La sensibilité au mécillinam était significativement meilleure qu'à tous les autres agents sauf la ciprofloxacine (P<0,001, test de McNemar). Les organismes moins sensibles au mécillinam étaient les genres *Citrobacter*, *Pseudomonas aeruginosa* et *Providencia*.
CONCLUSIONS : Les isolats des voies urinaires à Gram négatif dans la communauté demeurent extrêmement sensibles au mécillinam et à la ciprofloxacine, mais bon nombre ont acquis une résistance au triméthoprime-sulfaméthoxazole. Des études plus approfondies sont requises pour déterminer la signification clinique de ces résultats.

Acute urinary tract infections (UTIs) remain one of the most common problems for which patients seek medical treatment in the community. An estimated 10% to 20% of women will experience at least one infection during their lifetime (1). Fortunately, most episodes of uncomplicated UTIs do not result in long term sequelae. Appropriate antimicrobial treatment for UTIs increases the probability of suppression and cure (2,3) .

More than 90% of UTIs are due to enteric Gram-negative organisms, of which more than 80% are *Escherichia coli* (4,5). Current management guidelines recommend empirical therapy for acute, uncomplicated lower UTIs in young women (2,3). In typical cases, a urine culture is not necessary. Although this approach to management is simple and relatively cost effective, it is dependent on having an antimicrobial agent that is safe and to which most causative organisms are susceptible. Recent guidelines from the Infectious Disease Society of America (6) have recommended three days of treatment with trimethoprim/sulfamethoxazole or trimethoprim alone for the empirical therapy of acute uncomplicated cystitis. In areas where the prevalence of resistance to these agents is more than 10% to 20%, the guidelines recommend the use of a fluoroquinolone. This is supported by a recent study by Talan et al (7), which showed that in patients with acute uncomplicated pyelonephritis, resistance to trimethoprim/sulfamethoxazole was associated with a significantly greater bacteriological and clinical failure rate. However, reports of increasing resistance of Gram-negative bacteria to trimethoprim/sulfamethoxazole, trimethoprim and amoxicillin, as well as concern about the potential for increasing resistance to fluoroquinolones with increasing use, emphasize the need for alternative agents (2,8). Mecillinam is a novel oral beta-lactam antibiotic with considerable in vitro activity against the *Enterobacteriaceae* family (5,9). Although this agent has been available for years, few clinical trials have evaluated its efficacy or in vitro activity against community Gram-negative uropathogens (5,10-12). Thus, the purpose of this study was to determine the susceptibility of community outpatient Gram-negative urinary tract isolates to mecillinam and compare this with other commonly used oral agents for the treatment of acute uncomplicated cystitis.

MATERIALS AND METHODS

Between July and December 1997, 2000 consecutive community Gram-negative urinary tract isolates were collected from patients presenting to family physicians offices or outpatient clinics in southern Ontario. Urine specimens were collected for culture and sensitivity testing at the discretion of the physician, and not solely for the purpose of this study. Specimens were initially processed by a private laboratory servicing outpatient offices and clinics. Only those isolates that were deemed to be significant urinary pathogens by standard laboratory criteria were included (13) and were subsequently sent to the Department of Microbiology at Mount Sinai Hospital (Toronto, Ontario) for susceptibility testing for the study. All isolates were identified using standard laboratory methods. Susceptibility testing against mecillinam, ampicillin, trimethoprim/sulfamethoxazole, nitrofurantoin and ciprofloxacin was performed using agar dilution methodology. The breakpoints for ampicillin, trimethoprim/sulfamethoxazole, nitrofurantoin and ciprofloxacin were those published by the National Committee for Clinical Laboratory Standards approved document M7-A4 (14). The mecillinam susceptibility and resistance breakpoints used were less than 16 mg/mL and 16 mg/mL or greater, respectively. *E coli* ATCC 25922 and *Pseudomonas aeruginosa* ATCC 27853 were used as control strains, as recommended by the National Committee for Clinical Laboratory Standards (14). The susceptibility of mecillinam was compared with the susceptibility of the other agents using McNemar's test, with exact calculation of the test probability. Exact 95% CIs for percentages were calculated by using the F distribution (15,16).

RESULTS

Of the 2000 consecutive community Gram-negative isolates, 1832 (91.8%) were *E coli*, 78 (3.9%) were *Klebsiella*

species, 41 (2.0%) were *Proteus* species, and the remainder (2.3%) were other Gram-negative organisms. Table 1 illustrates the activity of the different antibiotics against all 2000 urinary tract isolates. Mecillinam's activity was significantly better (P<0.001, McNemar's test) than that of ampicillin, trimethoprim/sulfamethoxazole and nitrofurantoin but was inferior to ciprofloxacin. Table 2 shows the susceptibility of the various antimicrobial agents by organism. Against *E coli*, mecillinam had significantly greater activity than trimethoprim/sulfamethoxazole and ampicillin, and had comparable activity with nitrofurantoin and ciprofloxacin. Mecillinam maintained significant activity against organisms that were either susceptible or resistant to the other antimicrobial agents tested (Table 3).

TABLE 1
Activity of antibiotics against 2000 Gram-negative urinary tract isolates

	Percentage of susceptible isolates (95% CI)	Comparison with activity of mecillinam (McNemar's Test)
Mecillinam	98.8 (98.2 to 99.2)	
Ampicillin	77.0 (75.0 to 78.8)	P<0.001
Ciprofloxacin	100.0 (99.7 to 100.0)	P<0.001
Trimethoprim/ sulfamethoxazole	91.6 (90.3 to 92.8)	P<0.001
Nitrofurantoin	95.4 (94.3 to 96.2)	P<0.001

DISCUSSION

Our results suggest that most community Gram-negative urinary tract isolates remain susceptible to mecillinam and that this agent can be used for the empirical therapy of acute uncomplicated lower UTIs in the community. It has significantly better activity than all other agents tested except for ciprofloxacin. Compared with ampicillin, a commonly used beta-lactam antibiotic for the treatment of UTIs in pregnant women (17), mecillinam had significantly better activity against both ampicillin-sensitive and ampicillin-resistant isolates. This likely reflects the fact that mecillinam preferentially binds to penicillin-binding protein 2 in Gram-negative isolates, whereas other beta-lactams preferentially bind to penicillin-binding proteins 1a, 1b or 3 (18). As well, mecillinam has been shown to resist hydrolysis by beta-lactamases and thus has greater antibacterial potency against the *Enterobacteriaceae* family than other beta-lactam antibiotics (19). The relatively high rate of in vitro activity of mecillinam was also demonstrated for both susceptible and resistant isolates to trimethoprim/sulfamethoxazole and nitrofurantoin. The increased rates of resistance to trimethoprim/sulfamethoxazole may reflect the fact that it is one of the most commonly prescribed antibacterial agents in Canada for the treatment of uncomplicated UTIs, whereas mecillinam has not been used in Canada (20).

In a recent study of 2000 outpatient urinary tract isolates collected from tertiary care hospitals from across Canada, Zhanel et al (12) reported resistance rates for *E coli* that were significantly higher than those found in our study for ampicillin (41% versus 18%), mecillinam (7.4% versus 0.3%) and trimethoprim/sulfamethoxazole (18.9% versus 9.2%). Similar differences were noted among other Gram-negative isolates. These higher rates of resistance reported by Zhanel et al likely reflect the different patient populations studied. Although both studies were completed with outpatients, those patients in the study by Zhanel et al (12) presented to a tertiary care hospital, whereas those in our study were patients seen in family physician offices and outpatient clinics. Patients presenting to a tertiary care hospital may have more complicated UTIs, may have recently been inpatients and, thus, exposed to more resistant hospital flora, or may have failed previous therapy, all of which may account for the increased resistance compared with patients with simple uncomplicated UTIs presenting to their family physician. Because clinical data were not collected in this study or reported in the study by Zhanel et al (12), we could not determine any differences between the two patient populations to account for the differences in resistance rates. A similar trend toward higher resistance rates among outpatient urinary tract isolates received at a university microbiology laboratory and those from general practice has been noted previously (10). The university laboratory reported resistance rates that were three to four times higher for mecillinam and nitrofurantoin than those in general practice. Together with our results, this suggests that one must carefully interpret reported rates of resistance when selecting an antimicrobial agent for therapy of UTIs in the community. Reports from tertiary care laboratories may overestimate resistance rates in the community, even though the population studied may be outpatients.

TABLE 2
In vitro susceptibility of community Gram-negative uropathogens to selected antimicrobial agents

		Percentage of susceptible organisms by antibiotic (n)				
Organism	**n (%)**	**Ampicillin**	**Trimethoprim/sulfamethoxazole**	**Nitrofurantoin**	**Ciprofloxacin**	**Mecillinam**
Escherichia coli	1832 (91.8)	82.0 (1502)	91.8 (1681)	99.5 (1822)	100 (1832)	99.7 (1827)
Klebsiella spcies	78 (3.9)	0.0 (0)	97.4 (76)	69.2 (54)	98.7 (77)	100 (78)
Enterobacter species	19 (0.9)	0.0 (0)	100 (19)	63.0 (12)	100 (19)	100 (19)
Proteus species	41 (2.0)	92.7 (38)	82.9 (34)	4.9 (2)	100 (41)	97.6 (40)
Citrobacter species	14 (0.7)	0.0 (0)	100 (14)	100 (14)	100 (14)	92.8 (13)
Pseudomonas aeruginosa	7 (0.3)	0.0 (0)	0.0 (0)	0.0 (0)	100 (7)	57.1 (4)
Providencia species	5 (0.2)	0.0 (0)	100 (5)	0.0 (0)	100 (5)	0.0 (0)
Morganella morganii	4 (0.2)	25 (1)	100 (4)	75 (3)	100 (4)	100 (4)

TABLE 3
Activity of mecillinam against antibiotic-susceptible and resistant Gram-negative uropathogens

	Number of isolates	Number of mecillinam-susceptible isolates	Percentage of mecillinam-susceptible isolates (95% CI)
Ampicillin			
Susceptible	1539	1535	99.7 (99.3 to 99.9)
Resistant	461	441	95.7 (93.4 to 97.3)
Ciprofloxacin			
Susceptible	1999	1975	98.8 (98.2 to 99.2)
Resistant	1	1	
Trimethoprim/ sulfamethoxazole			
Susceptible	1832	1819	99.3 (99.8 to 99.6)
Resistant	168	157	93.5 (88.6 to 96.7)
Nitrofurantoin*			
Susceptible	1889	1880	99.4 (99.1 to 99.8)
Resistant	92	78	84.8 (75.8 to 91.4)
Total	2000	1976	98.8 (98.2 to 99.2)

**1981 isolates evaluable for this analysis*

Resistance rates in our study were highest among organisms such as *P aeruginosa*, *Providencia* species and *Citrobacter* species. Fortunately, these organisms are relatively uncommon causes of community-acquired lower UTIs, accounting for only 1.2% of all isolates in our study. The relatively high rates of susceptibility for most common organisms, such as *E coli*, suggest that the empirical use of mecillinam for the treatment of uncomplicated outpatient UTIs would be successful. Our results are consistent with a previously reported Canadian study that showed that mecillinam had significantly better activity than ampicillin and trimethoprim/sulfamethoxazole against urinary tract Gram-negative isolates (21). In fact, mecillinam was active against 91.9% of ampicillin-resistant *E coli* and 95.9% of trimethoprim/sulfamethoxazole-resistant *E coli*. Although mecillinam has little in vitro activity against Gram-positive organisms and these were not included in our study, some studies have demonstrated the clinical efficacy of mecillinam in the treatment of uncomplicated lower UTIs due to organisms such as *Staphylococcus saprophyticus* (22,23). Further clinical studies are required to determine whether the in vitro susceptibility of mecillinam translates into clinically effective therapy, especially in a three-day drug regimen as is currently recommended for trimethoprim/sulfamethoxazole and ciprofloxacin.

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