ANTIMICROBIAL DRUGS EVALUATION FOR URINARY TRACT INFECTIONS

REPORT 1 : ACUTE UNCOMPLICATED URINARY TRACT INFECTIONS AND CHRONIC COMPLICATED URINARY TRACT INFECTIONS

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Whenever new antimicrobial drug are being developed, phase 2 and phase 3 studies are done to evaluate the effectiveness of the drug against urinary tract infections. There is no world-wide standardized method of evaluating antimicrobial drugs. Based on the frequency of bacterial species present in urine, I propose that complicated urinary tract infections accompanied by an underlying disease of the urinary tract, and uncomplicated urinary tract infections should be considered as two separate entities and appropriate and individual investigative procedures be applied.

Various therapeutic agents against urinary tract infections have been developed. Studies to evaluate the clinical effectiveness and safety of each newly developed drug are conducted, without exception, prior to placing these drugs on the market. However, a generally accepted world-wide standardized method of evaluating such drugs has long been awaited. Although there are antimicrobial drugs for which a somewhat different approach to evaluation is required, there are problems for which a standardized evaluation can be made. Whether or not an underlying disease is present in the host, and the frequency of bacterial species isolated from urine, from the standpoint of the microorganism involved are common problems.

MATERIALS

The basis of this study was the frequency in which microorganisms were isolated from urine in clinical studies in conjunction with a phase 2 study during the development of a new antimicrobial drug. The findings in case of 5 different compounds prescribed for acute uncomplicated cystitis from 1973 through 1981[1)~5)] and 17 drugs[6)~22)] effective for chronic complicated cystitis from 1975 through 1979 have been reported.

RESULTS

E. coli was seen in 782 out of 1,039 strains (75.2%) of acute uncomplicated cystitis. Others included 91 strains of staphylococci (8.7%), 43 strains of *Proteus* sp. (4.1%), and 28 strains of *Klebsiella* (2.2%) (Table 1).

Serratia was the infective organism detected most frequently, that is 77 out of 390 strains (19.7%) in cases of chronic complicated cystitis. Others included 61 strains of *E. coli* (15.6%), 44 strains of *Pseudomonas aeruginosa* (11.2%) and 31 strains of *Enterobacter* (7.9%) (Table 2).

DISCUSSION

There are various methods of evaluating a new

Table 1 Bacteria isolated from urine of patients with acute uncomplicated urinary tract infections

Bacteria	No. of Strains	%
Staphylococcus	91	8.7
Enterococcus	20	1.9
Gram positive coccus	3	0.3
E. coli	782	75.2
Klebsiella	28	2.2
Proteus sp.	43	4.1
Citrobacter	9	0.8
Enterobacter	13	1.2
Pseudomonas aeruginosa	12	1.1
Acinetobacter	4	0.3
Gram negative bacillus	18	1.7
Not identified	16	1.5
Total	1,039	100.0

Table 2 Bacteria isolated from urine of patients with chronic complicated urinary tract infections

Bacteria	No. of Strains	%
Staphylococcus	18	4.6
Enterococcus	18	4.6
Gram positive coccus	28	7.1
E. coli	61	15.6
Klebsiella	17	4.3
Proteus sp.	23	5.8
Citrobacter	25	6.4
Enterobacter	31	7.9
Serratia	77	19.7
Pseudomonas aeruginosa	44	11.2
Glucose nonfermentative gram negative rod	23	5.8
Gram negative bacillus	27	6.9
Total	390	100.0

antimicrobial drug against urinary tract infections. One extreme method is the choice of the drug by the individual physician-in-charge. This lack of objectivity may sometimes detract from a proper evaluation. Another extreme method is to use minimum inhibition concentration (MIC) values of the antimicrobial drug against the causative microorganism. In such cases, an antimicrobial drug is determined to be inadequate when the isolated microorganism is over a certain MIC level. Therefore, this method is proper only for cases in which the microorganism is isolated below a certain MIC value and is based only on the antimicrobial potency of the antibiotic being tested, thereby allowing for on objective assessment. However, the evaluation of an antimicrobial drug against urinary tract infections should not be based totally on its antimicrobial potency but should include the degree to which the drug is concentrated in the urinary tract, the underlying disease of the urinary tract, the presence or absence and to what degree the urine stream is disturbed. It should also include the interaction between the antimicrobial drug and phagocytosis, and other complex factors.

Evaluation for a new antimicrobial drug should take into consideration the presence or absence and the degree of underlying disease within the urinary tract of the individual in question and I have advocated this approach since 1965[23]. Most uncomplicated urinary tract infections in the absence of an underlying disease or urinary stream disturbance are either acute or an initial infection. Complicated urinary tract infections with underlying diseases of the urinary tract and disturbances of the urinary stream are most often a re-infection or a chronic infection that has already been treated with antimicrobial drugs. This has much to do with the frequency of isolation of the causative organism. *E. coli* is most often isolated in 75.2% of the cases involving acute uncomplicated cystitis, whereas it is isolated in only 15.6% involving chronic complicated cystitis. This means that a considerable clinical efficacy is expected in the case of acute uncomplicated cystitis, if the most effective antimicrobial drug is prescribed. However, there will be less efficacy in cases of chronic complicated cystitis, even if the antimicrobial drug is administered.

Therefore, the evaluation of any new antimicrobial drug should be made on two main factors, a) acute uncomplicated urinary tract infections and b) chronic complicated urinary tract infections, as different disease entities. In doing so, one would take into consideration the underlying disease of the urinary tract, the presence or absence and to what degree the urine flow is disturbed and the species and frequency of the causative organisms. This method of evaluation has been approved by the Urinary Tract Infection Committee, in Japan[24].

Investigative procedures in the complicated urinary tract infections will be reported elsewhere.

REFERENCES

1) KUMAZAWA, J., et al.: Effect of Cephradine in acute simple cystitis—Comparative test by double blind method—. Chemotherapy 23 : 409～429, 1975
2) KUMAZAWA, J., et al.: Clinical study of Talampicillin in urinary tract infections by double-blind method. Jpn. Ass. Infect. Dis. 49 : 440～457, 1975
3) KUMAZAWA, J., et al.: Clinical study of Pipemidic acid in simple urinary tract infections by double blind method. Nishinihon J. Urol. 38 : 112～134, 1976
4) ISHIGAMI, J. & J. KUMAZAWA et al.: Clinical evaluation of AB-206 in acute simple cystitis—A comparative study with piromidic acid by a randomized double blind method—. Nishinihon J. Urol. 41 : 201～221, 1979
5) MOMOSE, S. & J. KUMAZAWA et al.: Clinical evaluation of C-AMOX in acute simple cystitis—a double blind comparative study of

C-AMOX and Amoxicillin—. Nishinihon J. Urol. 43 : 1305～1315, 1981
6) HIEDA, S. & J. KUMAZAWA et al.: Clinical studies on KW-1062 in complicated urinary tract infections. Chemotherapy 25 : 2235～2238, 1977
7) KUMAZAWA, J., et al.: Clinical experience of T-1220 in urinary tract infections. Chemotherapy 25 : 1401～1407, 1977
8) KUMAZAWA, J., et al.: Clinical evaluation on Ticarcillin in urological field. Chemotherapy 25 : 2867～2872, 1977
9) HIEDA, S. & J. KUMAZAWA et al.: Clinical studies on Cefoxitin in complicated urinary tract infections. Chemotherapy 26 (S-1) : 581～586, 1978
10) KUMAZAWA J., et al.: Clinical experience of PC-904 on complicated urinary tract infections. Chemotherapy 26 (S-2) : 468～472, 1978
11) IGUCHI, A. & J. KUMAZAWA et al.: Clinical experience of Cefamandole in complicated urinary tract infections. Chemotherapy 27 (S-5) : 523～532, 1979
12) KUMAZAWA, J., et al.: Experience with Cefuroxime in the treatment of chronic complicated urinary tract infection. Chemotherapy 27 (S-6) : 574～579, 1979
13) NAKASU, H. & J. KUMAZAWA et al.: Clinical efficacy of cefaclor on urinary tract infection. Chemotherapy 27 (S-7) : 614～624, 1979
14) KUMAZAWA, J., et al.: Clinical experience of Cefotaxime in complicated urinary tract infections. Chemotherapy 28 (S-1) : 802～815, 1980
15) KUMAZAWA, J., et al.: Clinical experience of Cefadroxil in urinary tract infections. Chemotherapy 28 (S-2) : 379～385, 1980
16) NAKAMUTA, S. & J. KUMAZAWA et al.: Clinical evaluation of Cefroxadine on urinary tract infections. Chemotherapy 28 (S-3) : 448～453, 1980
17) MIZUNOE, Y. & J. KUMAZAWA et al.: Clinical experience of Cinoxacin on urinary tract infections. Chemotherapy 28 (S-4) : 318～326, 1980
18) UOZUMI, J. & J. KUMAZAWA et al.: Clinical Experience of Ceftizoxime in urinary tract infection. Chemotherapy 28 (S-5) : 777～788, 1980
19) NAKAMUTA, S. & J. KUMAZAWA et al.: Experience with Cefoperazone in the treatment of chronic complicated urinary tract infection. Chemotherapy 28 (S-6) : 755～758, 1980
20) NAKAMUTA, S. & J. KUMAZAWA et al.: Experience with 6059-S in the treatment of chronic complicated urinary tract infection. Chemotherapy 28 (S-7) : 850～858, 1980
21) NAKAMUTA, S. & J. KUMAZAWA et al.: Clinical experience of Cefmenoxime in chronic complicated urinary tract infection. Chemotherapy 29 (S-1) : 877～887, 1981
22) NAKAMUTA, S. & J. KUMAZAWA et al.: Clinical experience of KW-1070 (Fortimicin) in urinary tract infections. Chemotherapy 29 (S-2) : 616～630, 1981
23) MOMOSE, S. & J. KUMAZAWA : Clinical features of urinary tract infection., 1 st ed. Kanahara, Tokyo, 1965
24) OHKOSHI, M. & N. KAWAMURA (The UTI Committee, Japan) : Criteria for evaluation of clinical efficacy of antimicrobial agents on urinary tract infection. Chemotherapy 28 : 321～341, 1980

尿路感染症に対する抗菌剤の評価方法

第1報：急性単純性尿路感染症と慢性複雑性尿路感染症

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新抗菌剤が開発されるたびに，その尿路感染症に対する有用性について phase 2, phase 3 の数多くの報告がなされている。しかしながら，その評価方法は世界的に画一されたものはまだ認められない。私はここに，尿路に基礎疾患を有しない単純性尿路感染症と基礎疾患を有する複雑性尿路感染症は別々に検討すべきことを提唱した。