The Korean Journal of Internal Medicine
Vol. 10, No. 1, January, 1995

The Incidence of Drug Resistant Tuberculosis in 1279 Korean Patients

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Objectives : *In the past decade, the incidence of tuberculosis has been decreased in Korea and the nationwide survey of tuberculosis from 1965 through 1990 suggested a declining tendency of resistant organisms. But the prevalence rate of multidrug resistance of Mycobacterium tuberculosis is still a serious problem in Korea, and the aim of this study is to check the drug resistance pattern in the patients visiting University Hospital, the 3rd referral center.*

Methods: *We reviewed 1279 cases(522 female, 757 male, mean age 39.4± 16.7) of bacteriologically proven tuberculosis seen during the period from 1986 to 1992 retrospectively. Of 1093 patients, who were indentified in previous medical history, 454(41.5%) had a history of prior antituberculous chemotherapy.*

Results: *Resistance rate(resistant to 1 or more drugs) was 33.9%. Eleven percent of patients had resistance to a single drug(INH : 80.6%). Twenty two percent of patients had resistance to 2 or more drugs. Resistance rate is higher(47.4%) in the patients with a history of prior treatment than without a history(25.5%).*

Conclusions: *These data suggest that the high rate of multidrug resistance in Korea did not show any decreasing tendency. So, mycobacterial culture and sensitivity tests should be recommended at initial treatment of tuberculosis and potent antituberculosis drugs are strongly recommended.*

Key Words : *Tuberculosis, Multidrug resistance*

INTRODUCTION

Drug resistance has been a very serious problem for treatment and eradication of tuberculosis in Asia, including Korea. And the prevalence of drug resistance has a close inverse relationship with the efficacy of antituberculous treatment regimens. Also, multidrug resistant tuberculosis is a fatal disease because the mortality rate was reported as high as 20% to 70% depending on underlying diseases, especially AIDS[2,3].

Surveillance of drug resistance in Korea during the period from 1965 through 1990 suggested declining proportions of patients infected with resistant organisms in the national tuberculosis prevalence surveillance(NTPS)[1]. But the total number of the culture proven cases was small in these studies and also the pattern of drug resistance among the patients visiting University Hospital, the 3rd referral center, may be different from the nationwide survey. So, we analyzed the drug resistant pattern of 1279 patients who had positive culture and sensitivity test for *Mycobacterium tuberculosis* during the period from 1986 through 1992, and compared data with nationwide survey.

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MATERIALS AND METHODS

1. *M. Tuberculosis* Isolates

The study population consisted of 1279 patients who were diagnosed as tuberculosis by culture with sensitivity test at Inje University, Paik Hospital, from 1986 through 1992. Different sources of specimens from sputum, broncho scopic washing fluid, pleural fluid, lymphnode, pus, ascitic fluid, cerebrospinal fluid and several

Table 1. Sources of Specimens

SPECIMENS	CASES(%)
Sputum	1078(84.2%)
Bronchial washing	69(5.4%)
Pleural fluid	27(2.1%)
Lymphnode	38(3.0%)
Cerebrospinal fluid	10(0.8%)
Others*	57(4.5%)
TOTAL CASES	1279

*Others : bone, intestine, soft tissue, pus and ascitic fluid, stool, urine, etc.

Table 2. Preinspissation Critical Concentration of Drug

Isoniazid(INH)	0.2 ug/ml
Rifampicin(RMF)	32.0 ug/ml
Pyrazinamide(PZA)	100.0 ug/ml
Ethambutol(EMB)	2.8 ug/ml
Streptomycin(SM)	10.0 ug/ml
Kanamycin(KM)	50.0 ug/ml
Cycloserine(CS)	40.0 ug/ml
p-aminosalicylic acid(PAS)	1.0 ug/ml
Prothionamide(PTA)	56.0 ug/ml
Tuberactinomycin(TM)	50.0 ug/ml
Ofloxacin(OFX)*	3.0 ug/ml

*Ofloxacin had been excluded from drug sensitivity tests during late 1991.

tissues showed growth of *M. tuberculosis*. Among them, the sputum was the major source (84.2%). (Table 1)

2. Drug sensitivity tests

When *M. tuberculosis* was identified by culture, every drug sensitivity test was performed at the KNTA(Korean National Tuberculosis Association).

The procedure of drug sensitivity tests was based on the absolute concentration method described by Canetti et al. with a little modification of inoculum preparation and size by the KNTA[5]. The tests were done in the Lowenstein-Jensen Medium. The drugs were added before inspissation at the concentrations noted below(Table 2).

3. Statistical analyses

The statistical significance of observed variables in clinical characteristics including age differentiation, annual trend of multiple drug resistance and different specimens was examined using the chi-square test. To evaluation for differences between the incidence of patients with or without a history of prior treatment for tuberculosis, odds ratio with 95 percent confidence intervals was calculated separately for each variables using SAS software.

Table 3. Demographic Profiles of Patients

	Total	Drug Resistance	No Resistance
Number	1279	434(33.9%)	854(66.1%)
Age(years)	39.1±17.3	39.4±16.6	38.8±17.9
Gender (male/female)	757 : 522	262 : 172	495 : 350

Table 4. Drug Resistance Rates of *M. tuberculosis*

Drugs	No. of cases	rate
1 drug	151	11.8%
2 drugs	101	7.9%
3 drugs	70	5.4%
4 drugs	29	2.3%
5 drugs	25	2.0%
6 drugs	14	1.1%
7 drugs	16	1.3%
8 drugs	15	1.2%
9 drugs	13	0.9%

Table 5. Age Differentiation in Resistance Rates

Age(years)	Total Cases	Resistant Cases(Rate %)
under 20	141	34(24.1%)*
21-30	349	109(31.2%)
31-40	236	91(38.6%)
41-50	161	66(40.9%)
51-60	171	59(34.5%)
over 61	221	75(33.9%)
Total	1279	434(33.9%)

*$p<0.05$

Table 6. Annual Trend of Drug Resistance in Tuberculosis Cases

Year	Total Cases	Resistant Cases(Rate)
1986	94	32(34.4%)
1987	189	64(33.9%)
1988	182	64(35.0%)
1989	166	47(28.3%)
1990	177	59(33.3%)
1991	183	58(31.7%)
1992	288	110(38.2%)
Total	1279	434(33.9%)

RESULTS

Demographic data were obtained for every patient and are summarizied in Table 3.

The overall prevalence of drug resistance rate (resistant to 1 or more drugs) was 33.9%. Elev-

en point eight percent was resistant to single antituberculosis drug and resistance rate to 2 drugs was 7.9%(Table 4).

There was no difference in the prevalence of drug resistance rate between groups above 60 years of age and below 60 years(Table 5). But the resistance rate of younger aged group(under 20 year old) is significantly lower than any other groups.

The average rate of drug resistance shows no significant change during the period from 1986 though 1992(Table 6).

Table 7. The Differences between the Incidence of the Patients with or without a History of Prior Treatment for Tuberculosis

History / Sensitivity	History of Prior treatment: Yes	No	Total No.
Resistant cases(%)	215(47.4)	163(25.5)	378(34.6)
All sensitive(%)	239(52.6)	476(74.5)	715(65.4)
Total No.	454(41.5%)	639(58.5)	1093

† Odds ratio=2.627(95% confidence interval, 2.034-3.394)

†† Chi-square test(x^2=56.003, p<0.001)

The information about the past medical history was available in 1093 patients and, among them, 454(41.5%) had a prior antibuberculous treatment. The prevalence of drug resistance in the patients with a previous antituberculous treatment(47.4%) was significantly higher than the patients without previous antituberculous treatment (25.5%). The crude odds ratio(95% Confidence Interval) was 2.627(2.034-3.394)(Table 7).

Data for the prevalence of individual drug resistance during the period of 1986-1992 is shown in Table 8. The more commonly used regimens, like in INH, RMP, EMB, and SM, showed higher rate of resistance.

The resistant rate was variable but the resistance to ofloxacin, KM, and prothionamide has been significantly increased during the study period. In contrast, decreasing tendency of resistance to SM has been decreased probably due to avoidance of practice. The resistance rate to one drug was 11.8%. INH was the most common single agent(82% of single drug resistance). And the prevalence of resistance to two drugs was 7.9% and usually in combination with INH and

Table 8. Annual Variation of Individual Drug Resistance Rates

Drugs	No. of cases	%	1986	1987	1988	1989	1990	1991	1992
INH	350	27.4	23.7%	27.5%	31.7%	24.7%	30.5%	32.0%	28.8%
RMP	164	12.8	9.7	14.3	14.2	5.4	17.5	14.4	15.3
EMB	137	10.7	7.5	12.7	10.9	12.7	13.0	8.8	10.8
SM	116	9.1	16.1	12.7	10.9	7.8	9.6	5.6	6.9
KM	84	6.6	4.3	7.9	6.0	2.4	6.8	10.4	8.7
PZA	78	6.1	3.2	5.3	4.9	2.4	5.1	5.6	12.8
CS	28	2.2	2.2	3.2	4.4	1.8	2.8	1.6	0.7
OFX	59	4.6	0	1.1	4.4	4.2	5.7	4.0	9.7
PAS	149	11.6	10.8	10.1	17.5	13.3	10.2	18.4	8.7
PTA	41	3.2	0	2.2	3.3	1.2	3.4	4.8	5.9
TUM	25	2.0	2.2	2.2	3.3	0.8	2.8	0.3	1.0

Table 9. Annual Trend of the Prevalence Multiple Drug Resistance

Drugs	No of cases(rate)	1986	1987	1988	1989	1990	1991	1992
HR	141(11.0%)	7.4	12.2	12.1	5.4	16.4	7.7	12.8
HS	97(7.6%)	10.6	10.1	9.9	6.6	7.9	3.8	6.3
HZ	66(5.2%)	3.1	4.2	3.8	2.4	5.1	1.6	11.1
HE	125(9.8%)	6.4	10.1	10.4	10.2	13.0	6.0	10.4
HRE	79(6.2%)	6.3	6.9	3.8	3.0	11.3	3.3	7.6
HRZ	57(4.5%)	2.2	3.7	3.3	1.8	4.5	1.6	9.7
HRS	50(3.9%)	5.3	5.3	5.5	3.0	5.1	2.2	2.4
HRZE	36(2.8%)	2.2	2.1	1.1	3.6	0.6	0	7.3
HRZS*	10(0.8%)	2.2	1.1	1.1	0	1.7	0	0.3
HRES	35(2.7%)	5.3	4.2	1.6	3.0	5.1	2.2	0.3

† H : isoniazid, R : rifampicin, E : ethambutol Z : pyrazinamide, S : streptomycin

*P<0.05

Table 10. Drug Resistance to Different Specimens

SPECIMENS	CASES	RESISTANCE(%)
Sputum	1078	34.0
Bronchial washing	69	*43.6
Pleural fluid	27	*12.5
Lymphnode	38	41.7
Cerebrospinal fluid	10	22.2
Others	57	29.1

*$p<0.05$

other drugs such as RFP, EMB, SM, PAS. The most important combination of antituberculous chemotherapy is INH and RFP and resistance rate to both drugs is 11.0%. According to NTPS, overall prevalence of drug resistance was decreased from 30.8%(1985) to 25.3%(1990), but our data showed no such trend. The pevalence of multidrug resistance varied significantly during the study period and no definite trend was found. Resistance to HRZS and HRZE was 0.8% and 2.8 % with stable or a declining trend(Table 9).

Drug resistance was also found in patients with extrapulmonary diseases(Table 10). Resistances in pleural fluid were significantly lower than those of sputum and bronchoscopic washing fluid.

DISCUSSION

Resistance to antituberculous drugs can occur as a random mutation, but much more frequently due to poor compliance of the patients and sometimes due to the inappropriate prescription by the physicians[6]. There are several well-known major causes of developing drug resistance, for example, erratic drug ingestion, omission of one or more of the prescribed agents, suboptimal dosage, poor drug absorption and insufficient number of active agents in a regimen[7,8].

The prevalence of drug resistance was quite low in western countries and it has been assumed as a problem of Asian countries. But with the advent of AIDS, not only the increasing prevalence of tuberculosis but also the problem of the drug resistance became an important health care issue even in western countries[2,9]. The resistance to antituberculous drug, especially to multiple drug has been a major problem in Korea. But the nationwide survey(NTPS) of tuberculosis in Korea, which has been held every 5th year since 1965, showed a decreasing tendency of multiple drug resistance(MDR) with prevalence of 15.0% in 1990[1]. But, in practice, we are still seeing many patients with MDR and we presume that the prevalence of MDR might be different in the patients visiting hospital. In our hospital, culture-sensitivity test was performed in almost all patients with tuberculosis, so we analyzed the data and compared it to NTPS.

We found that the prevalence of the drug resistance is quite high, actually higher than other previous reports. There are several possible reasons why the prevalence rate is higher in the hospital patients. First, there may be more patients with treatment failure; second, the patients who have severe and advanced diseases such as cavities or miliary tuberculosis will gather in the hospital; third, the number of the patients with recurrent diseases may be higher.

The previous studies suggested that the history of prior antituberculosis therapy and the presence of cavitary lesion were the most valuable predictors of the drug resistance and our data support this[10-12]. According to our results, the prevalence of the resistance in patients with prior treatment is significantly higher(47.4%) than without previous therapy(25.5%). In the survey of 31 States and large city laboratories in the U.S, Cauthen et al reported that the prevalence of the resistance to at least one antituberculous drug was 8% in never-treated patients and 23% in previously treated patients[13]. At California Hospital, Ben-Dov reported a much higher resistance rate(23% in never-treated patient and 59% in previously treated patients)[14].

And although the study period is short(7 years), the resistance rate is rather stable, not decreasing during this period. But one promising finding is that the resistance rate is significantly lower in young patients(under 20 years:24.1%) compared to other groups which suggests that we can decrease it in the future by proper management. The drug resistance was also found in the patients with extra-pulmonary diseases, but the 12.5% of drug resistance in the pleural fluid was significantlry lower than that of pulmonary and lymph node specimens. But the specimen from extrapulmonary source should be cultured because the prevalence of drug resistance in pleural fluid was significant.

Resistance to INH is the most frequent and it occurred as a single drug resistance or in combination with other drugs. The reported prevalence of INH resistance was variable from 3% to 33% depending on the ethnic groups, socioeconomic status or the severity of the underlying disease[15]. Berliner reported it as 17% in U.S.

Army Community Hospital, Seoul[16], it was 22.2% in NTPS, and Carpenter found that 33% of U.S. military patients in Korea had INH resistance[17].

In our patients, the average 27.4%(23.7-32%) had resistance to INH. Significant proportion(12.8 %) of the patients had resistance to RFP and it is very important because it is the essential component of short course chemotherapy of tuberculosis. Also, our data showed the prevalence of resistance to ofloxacin and prothionamide was increasing. Resistance to pyrazinamide showed an increasing tendency too. Fortunately, resistance to SM was decreasing, probably because of the avoidance of the drug due to hyper-sensitivity reaction in clinical practice. The drug resistance of tuberculosis is of importance for several reasons. it's influences are significant because first, the modest risk of failure of chemotherapy in individual patients; second, the production of further and more drug resistance; third, the community and nationwide public health problems due to the spread of drug resistant organisms. These problems may threaten a successful initial chemotherapy[18-20].

Moreover, small(6.5%) but significant percentage of the patients had resistance to 5 or more drugs, and most of them were resistant to major drugs. it is very difficult and sometimes impossible to treat them properly and we need new effective drugs urgently. The treatment of patients with pulmonary tuberculosis who have *M. tuberculosis* resistant strains to multiple antituberculosis drugs is very complicated, risky and of limited efficacy. Goble et al reported that the treatment failure rate of patients with multiple drug resistance was 46%[21]. In this study, we did not evaluate the effectiveness of treatment of multidrug resistant tuberculosis, but it might be done. Also we strongly recommend that drug sensitivity tests should be done for every patient with tuberculosis in Korea, including patients for initial treatment.

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