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Drug Resistance Analysis of Pasiniazid against Isoniazid-Resistant, Parasal-Resistant, Isoniazid and Parasal-Resitant, and Multidrug-Resistant

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Abstract

Objective: In view of the high INH resistance, we conducted in vitro drug susceptible test of Isoniazid (INH) and Parasal (PAS) and Pasiniazid (PA) to determine the cross-resistance of the three drugs.

Method: The proportion method on Lo¨wenstein–Jensen (L–J) medium was used to conduct antimycobacterial susceptibility testing of INH and PAS and PA to one hundred and ninety-seven clinical isolates of, including multidrug-resistant isolates.

Results: For INH-resistant isolates, PA sensitive rate was as high as 73.6%. The three PAS-resistant isolates were all susceptible to PA. 92% of the isolates resistant to INH and PAS simultaneously were resistant to PA. Most of the isolates susceptible to INH and PAS were also susceptible to PA. More than half of the MDR strains are still sensitive to PA. Almost all of the seventy PA-resistant isolates were also resistant to INH except one isolate. However, 34.3% of the seventy PA-resistant isolates were susceptible to PAS. For MDR isolates in this experiment, PA resistant rate was 46.2%.

Conclusion: PA showed lower susceptibility to the isolate resistant to INH and PAS simultaneously. PAS has strong anti-TB effect. INH is not recommended for the PA-resistant isolates. For single INH resistant cases or MDR cases, we can consider using PA instead of INH.

Keywords: Multidrug-resistant; Drug resistance; Pasiniazid; Isoniazid; Parasal

Introduction

Tuberculosis (TB) remains a major global health problem and ranks as the second leading cause of death from an infectious disease worldwide [1]. In 2013, an estimated 9.0 million people developed TB and 1.5 million died from the disease. Isoniazid (INH) is the first choice for the treatment of TB and it plays an important role in effective control of TB. However, the initial INH resistance rate had reached 17.6% and it was as high as 80.5% in retreatment patients [2,3]. Pasiniazid (PA) is a compound which is composed of Parasal (PAS) and INH. PAS binding the N site in INH molecular structure and delaying acetylation of INH. Some of the isolates which are resistant to INH are susceptible to PA [4,5]. PA is soluble and easily absorbed. Some clinicians take it as core drug for retreatment tuberculosis or drug-resistant tuberculosis and even multidrug-resistant tuberculosis to replace INH. But robust investigations of the potential therapeutic value of PA against drug-resistant are urgently needed. To address this need, we conducted this study of in vitro drug susceptible test of INH and PAS and PA on 197 (MTB) clinical isolates using the proportion method on Lowenstein-Jensen (L–J) medium and analyzed the cross-resistance of the three drugs. We also conducted drug susceptible test of PA on multidrug-resistant (MDR-TB) to find the value of clinical application of PA on MDR-TB.

Materials and Methods

Test isolates

A total of 194 clinical isolates of including INH-resistant strains and PAS-resistant strains and susceptible strains were obtained from the National Tuberculosis Reference Laboratory (Beijing, China).

Antimicrobial agents

The antimicrobial agents PA, INH, PAS were purchased from Sigma Chemical Company (St Louis, MO). Initial stock solutions of these antimicrobial agents were prepared according to manufacturers' instructions and stored at -70°C until use.

Antimycobacterial susceptibility testing

Antimycobacterial susceptibility testing was conducted using the proportion method on L–J medium. The L–J medium was impregnated with INH, PAS and PA, in conformity with the proportional technique as recommended by Clinical and Laboratory Standards Institute (CLSI) [6]. The critical test concentration for INH-resistant strains was 1 μg/ml and for PAS was 10 μg/ml according to the CLSI. For PA, there was no standard. In this study, we used 1 μg/ml as critical test concentration adopting the concentration of clinical absolute method of drug sensitivity test as reference.

Statistical analyses

Statistical analyses were conducted using SPSS statistical software (SPSS Statistics 17.0; SPSS Inc., Chicago, IL). Pearson's chi-square test was used for proportional comparisons among different subgroups. All p-values were two-sided with α=0.05.

Results

For INH-resistant isolates, PA sensitive rate was as high as 73.6% as shown in Table 1. The three PAS-resistant isolates were all susceptible to PA. While for the isolates which were resistant to INH and PAS simultaneously, PA sensitive rate was only 8%. Most of the isolates (98.1%) which were susceptible to INH and PAS were also susceptible

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Subgroup	Isolates	PA-resistant isolates	Resistant rate of PA (%)	Susceptible rate of PA (%)
INH-R/PAS-S	87	23	26.4	73.6
INH-S/PAS-R	3	0	0	100
INH-R/PAS-R	50	46	92	8
INH-S/PAS-S	54	1	1.9	98.1
MDR-TB	52	24	46.2	53.8

INH: Isoniazid; PAS: Parasal; PA: Pasiniazid; R: Resistant; S: Susceptible

Table 1: Drug resistance of Pasiniazid against the 194 clinical isolates.

to PA. The difference of the sensitive rate showed statistical significance (=1.2587E-21; =100.4259). Table 2 shows that almost all of the seventy PA-resistant isolates were also resistant to INH except one isolate. However, 34.3% of the seventy PA-resistant isolates were susceptible to PAS. The difference of the sensitive rate showed statistical significance (=1.2053E-06;=23.5687). In this experiment, more than half of the MDR strains (53.8%) were still sensitive to PA.

Discussion

Since the rate of INH-resistance is very high especially in retreatment pulmonary tuberculosis patients currently, the alternative medicine is urgently needed. In clinical practice, application of PA in the treatment of INH-resistant tuberculosis is still controversial. The treatment effect of PA for INH or PAS resistant tuberculosis is questioned. According to report, PAS binding the N site in INH molecular structure and delaying acetylation of INH to significantly increases the bactericidal effect of INH [7]. The effect of PA is obviously higher than that in PAS and INH hybrid in physical form [8]. According to manufacturers' instructions, the effectiveness of PA is about 5 times than the same dose of INH. Our results indicate that the susceptibility rate of INH-resistant MTB to PA was as high as 73.6%. Consequently, for a part of single INH resistant MTB, PA is still effective. Compared to INH, PA can cross the blood brain barrier easily into the cerebrospinal fluid and can penetrate the cell membrane to make the concentration of INH maintain a high level in a long time. PA can also be used in children with mild tuberculosis and other INH intolerant patients [9]. PA resistant rate was 46.2% of the MDR isolates in this experiment. Therefore, for single INH resistant cases or MDR cases, we can consider using PA instead of INH. Since all of the PA-resistant isolates were resistant to INH, INH is not recommended for the PA-resistant isolates. PAS have been rarely used clinically from the advent of short course chemotherapy. PAS-resistant rate of was only 2.8% [2]. Only three isolates of single PAS resistant strains were collected in this experiment. All was sensitive to PA at the concentration of 1 μg/ml. 34.3% of PA resistant isolates was susceptible to PAS, which indicated that PAS has strong anti-TB effect. The above result was probably related to the selection of critical test concentration

Drug	Resistant isolates (%)	Susceptible isolates (%)	Sum
INH	69 (98.6)	1 (1.4)	70
PAS	46 (65.7)	24 (34.3)	70

INH: Isoniazid; PAS: Parasal; PA: Pasiniazid

Table 2: Drug resistance of INH and PAS against PA-resistant clinical isolates.

to determine PA resistance. There was no national standard of critical test concentration for PA-resistant strains. In this study, we used 1 μg/ml as critical test concentration adopting the concentration of clinical absolute method of drug sensitivity test as reference. Our results indicate that PA showed lower susceptibility to the isolate resistant to INH and PAS simultaneously. So the application of PA in patients with INH and PAS simultaneously resistant has yet to be researched.

This study has several limitations that are worth noting. First, the sample size in this study was small, which limited the power of our analysis. Second, we used 1 μg/ml as critical test concentration since there was no national standard of critical test concentration for PA-resistant strains. Third, as far as we can see this was a rather prelimianry test, we need convincing clinical data to confirm the conclusion.

In conclusion, we found that for a part of INH- resistant MTB and MDR-TB, PA is still effective. In the area of high incidence of drug-resistant tuberculosis, we can consider using PA instead of INH.

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