In-vitro activity of erythromycin for the mycobacterium tuberculosis

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In-vitro activity of the erythromycin and standard tuberculosis drugs [streptomycin (SM), isoniazid (INH), ethambutol (EMB), rifamycin (RIF), thiasetazon (TH)] against 34 clinic isolates of myobacterium tuberculosis were studied by standard proportion method on Lowenstein-Jensen medium. The minimal inhibitory concentration (MIC) of erythromycin for 50% and 90% of the strains were 16 and 111.5 mg/L respectively. The strains were typed by standard biochemical methods. One of the strains was non tuberculosis mycobacterium Runyon Group III. The nontuberculosis mycobacterium was resistant against standard tuberculosis drugs and all the concentration of erythromycin. The cross-resistance was not seen between erythromycin and standard tuberculosis drugs. Because of high MIC values obtained erythromycin wouldn't be effective on mycobacterium tuberculosis. [Turk J Med Res 1993; 11(2): 59-61]

Key Words: Myobacterium tuberculosis, Erythromycin

Resistance against the standard tuberculosis (tb) drugs calls the necessity of antituberculous agents. So the new researchers are focused on new antituberculous agents which has an effect on the biosynthesis of mycolic acid, arabinogalactan, peptidoglycan, mycobactin without any diverse effect on the nonbacterial flora (1). The invitro studies in the treatment of drug resistant tb are thought to be satisfactory by the combination of ansamycin (rifabutin)), florocinolon (ofloxacin, ciprofloxacin) and the inhibitor of beta lactamase combined by beta lactame antibiotics (2-14). Previously, the invitro activities of antibiotics used in non-specific infections are studied for the mycobacteries and some of them are widely used in clinics (4,5,15-21). Erythromycin is an antibiotic which is obtained from the streptomyces erythreus strain. It is either in white or yellow crystal form which is soluble in 1/5 alcohole chloroform, ethyl alcohole, and 2M hydrochloric acid (The chemical forms are; salt, base and ester). The acidity of the stomach causes the cleavage of this compound which has a half life of 1.2-4 hours and it is tightly bound to the plasma proteins (64.5±0.4%). The total dose for a day is 1000-1500 mg and it can be divided into 2 or 3 dose during a day (22-24).

The purpose of this study is to investigate the in-vitro activity of erythromycin for the mycobacterium tuberculosis.

MATERIALS AND METHODS

The invitro activity of the erythromycin [the ester form (ethyl succinate)] obtained from ABFAR İlâç Sanayi TAŞ was tested on 34 clinic isolates. The Lowenstein-Jensen medium having drug concentration as 8, 16, 32, 64 and 128 mg/L were prepared seperately. Standard proportion method was used for the sensitivity test (25). Furthermore the sensitivity of all strains against erythromycin and other standard tuberculosis drugs (SM: 4-8 mg/L, INH: 0.2-1 mg/L, EMB: 2-4 mg/L, TH: 2-4mg/L, RIF: 20-40 mg/L) were tested. All cultures were incubated at 37°C for 3-4 weeks and standard biochemical tests were used in typing (26).

RESULTS

Table 1 shows the results of 34 clinic isolates. The strains were inhibited 15 (44%), 8 mg/L, 17 (50%), 16 mg/L, 20(59%), 32 mg/L, 26 (77%), 64 mg/L and 32 (94%) 128 mg/L by erythromycin. The minimal inhibitory concentration was defined as the last amount that inhibits the growth of the bacteries (MIC).

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Table 1. In-vitro susceptibility of tuberculosis strain to erythromycin

Erythromycin concentrations (mg/liter)	Susceptible strain Rates	
	Number	(%)
8	15	44
16	17	50
32	20	59
64	26	77
128	32	94

The drug concentration that inhibit the 50% and 90% of the strains were named as MIC 50 and MIC 90 respectively. According to the statistical results there was a significant linear relation between the erythromycin concentration and inhibition ratio (r-0.98, r2-0.96, t-3.18, p<0.05). Regression analysis indicated that MIC 50 as 16 mg/L and MIC 90 as 111.5 mg/liter (Figure 1). The typing results, also indicated that one of the 34 strains was nontuberculosis mycobacterium (Runyon Group III) and the rest were human type. Both nontuberculosis strain and one of the human type strains had resistance against all different concentrations of erythromycin.

The erythromycin resistant nontuberculosis strain had resistance against SM 4 mg/L, INH 0.2 mg/ilter, EMB 2 mg/liter, TH 2 mg/liter and RTF 40 mg/ilter. However in the human type nontuberculosis strain had a resistance to RIF and sensitive to SM, INH,EMB and TH. Twelve strains had RIF, two strains had SM+INH+RIF, two strains had TH+INH+RIF and one strain had INF+RIF resistance but the others were sensitive.

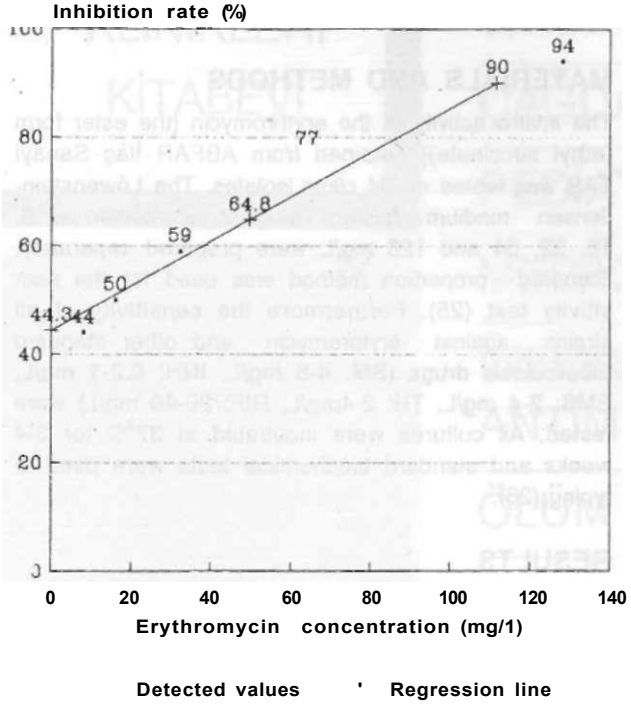

Figure 1. In-vitro activity of erythromycin for the mycobacterium tuberculosis.

DISCUSSION

Erythromycin has been mostly used in curing infectious disease with nonspecific casuses. In the 607 patients with acne 2x500 mg/day oral dose has been used during six month without any serious diverse effect (22). For the non-tuberculosis mycobacterial infections, erythromycin was used and good results were obtained. Collins and Uttey showed the effect of erythromycin in mycobacterium cansasii, mycobacterium xenopy, mycobacterium fortiutuma (27). Furthermore Hanson et al cured their patients with the combination of erythromycin and trimethoprim (28). Guest et al cured an 83 years old male patient having lung infections during 11 months, with (3x500 mg/day) erythromycin (29). However there are only few number of researches for the effect of erythromycin on tuberculosis. Gevaudan et al studied 41 strains (15 tb and 26 non-tb) and detected the MIC value of erythromycin as 32 mg/liter with a range of 16-128 mg/liter. For non-tb strains such as mycobacterium avium, chelonae, fortuitum, cansasii, marinium and xenopy; MIC values were 16, 64, 8, 1 mg/L respectively (5). Gorzynski et al searched the effect of clarithromycine on tb and compared this effect with quinolones and suggested the MIC value of erythromycine for tb as greather than 10 mg/L but couldn't give exact values for MIC 50 and MIC 90. However claritromycin was more effective than erythromycin, but less effective than quinolones (30).

In our study, the MIC value for the tb was in accordance with other studies. After the oral application of 2 g erythromycin, the serum concentration was 1.37 mg/liter (0.3-2.6 mg/liter) and in the bronchial secretion it's concentration was 0.59 mg/liter (0.125-2.49 mg/liter) (31). As seen from these results the MIC values for the tuberculosis couldn't be reached by the routine doses, so the in-vitro and in-vivo doses were different. Finally it was concluded that erythromycin was not effective on myobacterium tuberculosis.

Eritromisin'in tüberküloz basili üzerine in-vitro etkisi

Eritromisin'in tüberküloz (tb) basilinin 34 klinik izolatı üzerine in-vitro etkisi Lövvenstein-Jensen besiyerinde, standart proporsiyon yöntemi ile araştırıldı. Minimal inhibisyon konsantrasyonu (MIK) değerleri MIK50 16 mg/liter, MIK90 111.5 mg/liter olarak saptandı. Eritromisin ile birlikte standart tb ilaçları da (SM: stremptomisin, INH: isoniazid, EMB: etambutol, TH: tiasetazon, RIF: rifampicin) test edildi. Standart biyokimyasal testlerle tip tayini yapıldı. Klinik izolatlardan birisi non-tb (Runyon

Grup III)- Diğer 33'ü insan tipi idi. Non-tb suş, standart tb ilaçları ve eritromisin'in kullanılan bütün konsantrasyonlarına dirençliydi. İnsan tipi basillerden 17 suş bütün ilaçlara duyarlı, 12 suş sadece RIF'e 2 suş SM, INH, RIF, 2 suş TH, INH, RIF, 1 suş INH, RIF'e dirençli bulundu. Eritromisin ile standart tb ilaçları arasında çapraz direnç bulunamadı. Elde edilen yüksek MIK değerleri nedeniyle eritromisin tb basili üzerinde etkili olamayacağı kanısına varıldı.

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