TITLE: ACTIVITY OF LINEZOLID OR LEVOFLOXACIN WITH ANTITUBERCULOSIS DRUGS COMBINATIONS IN *Mycobacterium tuberculosis*

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ABSTRACT: Tuberculosis (TB) is a worldwide public health problem and requires a drug combination therapy of at least six months to treat the patient. Standard treatment uses isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA) and ethambutol (ETH). In recent decades, TB control has been severely compromised by the emergence of multidrug resistant (MDR) clinical isolates, which is resistant to INH and RIF. In the search for new treatment options, other drugs have been studied for using in TB therapy such as levofloxacin (LVX), moxifloxacin, linezolid (LNZ), amoxicillin-clavulanate, clarithromycin, thioridazine, clofazimina and others. In this sense, the objective of the present study was to evaluate the *in vitro* activity of LNZ or LVX combined with INH/RIF in *Mycobacterium tuberculosis*. The INH/RIF/LVX and INH/RIF/LNZ drugs combinations were tested in *M. tuberculosis* $H_{37}Rv$ (ATCC 27294) reference strain, one first-line drugs susceptible and 10 MDR clinical isolates by modified checkerboard method. The LNZ and LVX were used at ¼ Minimum Inhibitory Concentration (MIC) fixed concentrations in all assays. The INH and RIF were tested at concentrations ranging from 0.0002 mg/L to 400 mg/L and 0.0005 mg/L to 3,000 mg/L, respectively. MIC was defined as the lowest concentration of INH/RIF/LVX and INH/RIF/LNZ combinations, in which no visible bacillary growth was observed and the Fractional Inhibitory Concentration Index (FICI) were determined. FICI value ≤ 0.75, 0.75 - 4 and ≥ 4 were considered synergistic, indifferent and antagonistic, respectively. Synergisms of INH/RIF/LVX or INH/RIF/LNZ combinations were observed in 30 % and 40 % of the MDR clinical isolates studied, respectively. For the other isolates, there were a reduction of the RIF and INH combinations MICs values, however no synergism were observed. In this sense, the use of LVX and LNZ may contribute to the therapy of patients with TB, especially in MDR cases.

KEYWORDS: tuberculosis, multidrug-resistant, three-dimensional checkerboard