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Verapamil Effect on *Mycobacterium tuberculosis* Clinical Isolates Susceptibility Against First- and Second-Line Drugs Using MGIT 960

A Cross-Sectional Study

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Verapamil Effect on Mycobacterium tuberculosis Clinical Isolates Susceptibility Against First- and Second-Line Drugs Using MGIT 960

Running title: Verapamil in first and second line Anti tuberculosis Drugs

ABSTRACT

Background and Objective: With the expanding knowledge about efflux pumps contribution to the resistance mechanism of *Mycobacterium tuberculosis* has increased the attention to efflux inhibitors usage as adjuvants in tuberculosis therapy. Therefore, this study aimed to evaluate the effect and interaction between efflux inhibitor towards first- (isoniazid, streptomycin, rifampicin, ethambutol) and second-line (kanamycin, ofloxacin, capreomycin, moxifloxacin) antituberculoid drugs in *M. tuberculosis* susceptibility. **Materials and Methods:** Sixty-five *M. tuberculosis* isolates collected from sputum samples of tuberculosis patients in Makassar and exposed to anti-TB drugs at critical concentration in the presence or absence of verapamil (40μg/mL) using drug susceptibility test (DST) proportion method in Mycobacterium Growth Indicator Tube (MGIT) 960 System. **Results:** 14 isolates (21,54%) were mono-resistant, 20 isolates were MDR-TB (30,67%), 20 isolates (30,67%) were Pre XDR-TB, and 7 isolates (10,77%) were XDR-TB. There were eight drugs that were tested but only six drugs showed a decrease of *mean* growth unit in STR, INH, RIF, CAP, and MOXI after the addition of efflux pump inhibitor (synergy observed). The overall effect of verapamil towards all groups of drugs tested showed p value of

0,001 ($p<0,05$). **Conclusions:** The addition of verapamil plays a significant role in restoring the susceptibility of *M. tuberculosis* isolates.

Key words: Efflux pumps, Verapamil, Anti tuberculosis, Drug susceptibility test, *Mycobacterium tuberculosis*.

INTRODUCTION

Mycobacterium tuberculosis is the leading cause of global tuberculosis (TB) infection.[1] The emergence of *M. tuberculosis* strains bacteria that are resistant to first-line (called Multi Drug Resistant / MDR) and second-line drugs (called Extensive Drug Resistant / XDR) lessen the alternative of antibiotic use to treat TB disease.[2-7] Bacterial resistance to antibiotics is not caused by a single mechanism, but is a combination of genetic factors such as spontaneous mutations of target genes and the transfer of genetic elements; and intrinsic factors such as changes in permeability of bacterial cell barriers, presence of porins, and activation of efflux pump systems.[8-14]

In physiological conditions, efflux pump generates an important contribution to the phenotype of low level drug resistance due to the function of the protein efflux pump transporter which limits intracellular drug concentration.[15-17] Some components are known to have the potential to inhibit the efflux pump system, but the working mechanism of the inhibitor components in the cell is not yet clear.[3,16,17,18-25]