the functional native enzyme d-Ala-d-Ala ligase. Vancomycin induction of VanA or VanB ligase is thought to compensate for the absence of the native ligase by producing UDP-MurNAc-tetrapeptide-d-Lac, thereby allowing cell wall synthesis to proceed. This conclusion was reached because of the growth of VDE when supplemented with the dipeptide d-Ala-d-Ala in the absence of vancomycin.3-5

The strain of GDE described here is unique, not only because of its resistance to LY333328, but also because of its dependence on it for growth. Furthermore, the bacterium grew in the presence of glycopeptide antibiotics, but not in the presence of peptidoglycan precursors. The genetic mechanisms that are the basis of glycopeptide dependence in these mutants remain to be elucidated.

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References


In-vitro activity of N,N-dimethyl-2-propan-1-amines against Mycobacterium tuberculosis

A. O. De Souzaa, D. C. G. Ailyb, D. N. Satoe and N. Durán**

**Instituto de Química, Biological Chemistry Laboratory, Universidade Estadual de Campinas; bInstituto Adolfo Lutz, Campinas; cInstituto Adolfo Lutz, Ribeirão Preto, S.P.Brazil

*Corresponding author. Instituto de Química, Biological Chemistry Laboratory, Universidade Estadual de Campinas, C.P. 6154, Campinas, CEP 13083-970, S.P. Brazil.
E-mail: duran@iqm.unicamp.br

Sir,
The magnitude of endemic tuberculosis is increasing and it is estimated that 1.7 billion people worldwide are infected with Mycobacterium tuberculosis.1 In addition to an increase in the number of cases, the increasing incidence of multidrug resistant tuberculosis is one of the major public health challenges in the 1990s.2 The interaction between acquired immunodeficiency syndrome (AIDS) and tuberculosis has a major impact on the long-term survival of AIDS patients.3 Consequently, there is an urgent need to develop antimycobacterial drugs which may be more effective than the chemotherapy currently in use.

Recently, a series of N,N-dimethyl-2-propan-1-amine derivatives, 3-(4'-bromo[1,1'-biphenyl-4-yl]-3-(4'-(X-phenyl))-N,N-dimethyl-2-propan-1-amine, where X is H, Cl, Br, 1, CH3, OCH3, SO2CH3 or NO2, with excellent trypanocidal activities has been synthesized.4-6 These derivatives are substituted at the 4-position on the phenyl moiety and are obtained as a mixture of the E/Z isomers (nearly 1:1). In this study, we assayed the in-vitro activity of the 4-bromo derivative (X = 4-Br) and the unsubstituted derivative (X = 4-H), and their geometric E and Z isomers against M. tuberculosis (Figure).

The strains of M. tuberculosis (H37Rv, ATCC 25177) were grown in Middlebrook 7H9 broth (Difco, Detroit, MI, USA) at 37°C until the turbidity was equivalent to a McFarland no. 1 standard (3 × 108 cfu/mL). In order to determine the MIC, stock solutions of the drugs were freshly prepared in dimethyl sulphoxide (Sigma) at 1 g/L and serial two-fold dilutions were prepared in 7H9 broth (Difco) to yield final concentrations of 2 to 256 mg/L.
These tubes and control tubes containing no drug were inoculated with approximately $1.5 \times 10^5$ cfu/mL of *M. tuberculosis* and were incubated at 37°C for 10 days. The microorganisms that grew in the presence and in the absence of the drugs were measured by the visual turbidity method and the MIC was taken as the lowest drug concentration that allowed no visible growth.

To determine the MBC we used the subculture in a Lowenstein–Jensen (Difco) medium with the dilutions of drugs that were equal to or higher than the MIC of each studied drug. The values of the MIC and MBC the *N,N*-dimethyl-2-propen-1-amine (X = Br) derivative were 4 and 16 mg/L, respectively. The latter compound was twice as effective as the unsubstituted (X = 4-H) derivative, which had an MIC of 8 mg/L and an MBC of 32 mg/L. The MIC and MBC of the unsubstituted geometric Z isomer were 8 and 16 mg/L, respectively, while those of the E isomer were 16 and 128 mg/L, respectively.

Our results indicated that the 2-propen-1-amine derivatives have good bacteriostatic and bactericidal activity against *M. tuberculosis*. The bromo substitution (X = 4-Br) is also important for the antibacterial activity of these compounds in the same way as has occurred in Chagas’ disease.5 The unsubstituted Z isomer showed great potential in this regard and should thus be evaluated as a chemotherapeutic agent against *M. tuberculosis*. In vitro studies have been used to measure the activity of a drug against extracellular bacilli. Since mycobacteria infect and multiply in macrophages, it is necessary to improve the correlation between in-vitro MICs and MBCs of these drugs to their intracellular activity in experimentally infected macrophages. New 2-propen-1-amines are being synthesized in order to increase the antibacterial capacities, and in-vivo studies of these compounds in models of tuberculosis are in progress.

**Pharmacokinetics of cefuroxime in healthy volunteers: an update**


L. Massias*, C. Muller-Serieys*, R. Farinotti* and E. Bergogne-Bérézin*

Departments of *Pharmacy and *Microbiology, CHU Bichat-Claude-Bernard, 46 rue Henri-Huchard, 75877 Paris Cedex 18, France

*Corresponding author. Tel: +33-1-402-58527; Fax: +33-1-404-90475.

Sir,

After two decades, cefuroxime continues to be prescribed widely as treatment of patients with a broad range of community-acquired infections, particularly those affecting the respiratory tract. Pharmacokinetic studies of parenteral cefuroxime were first published between 1976 and 1978.1–3 The present study was undertaken to update the pharmacokinetics of this drug following a single dose given by the intramuscular (im) route and to evaluate the effects of the co-administration of lidocaine on these pharmacokinetic parameters. A secondary objective was to compare the plasma antibiotic concentrations of

**References**


