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Trypanocidal activity of novel alkanediamide-linked bisbenzamidines and bisbenzamidoximes

T. Huang[1,*], N. Kode[2], C. Bacchi[3], D. Rattendi[3], J.J. Vanden Eynde[2], A. Mayence[2], N. Yarlett[3], I. Londono[3]

[1] *Xavier University of Louisiana, New Orleans, LA, USA*
[2] *Xavier University of Louisiana, College of Pharmacy, New Orleans, LA, USA*
[3] *Pace University, Haskins Laboratories, New York, NY, USA*

Background: Human African trpanosomiasis (HAT) is caused by the protozoan parasites *Trypanosoma brucie gambiense (T.b.g)* and *Trypanosoma brucie rhodesiense (T.b.r)* and is usually fatal when left untreated. It is one of the most neglected tropical diseases in the world causing an estimated 50,000 deaths annually. Current drug therapy suffers from high toxicity, undesirable intravenous route of administration and emergence of parasite resistance. The present study is to evaluate the trypanocidal activity of a novel series of alkanediamide-linked bisbenzamidines and bisbenzamidoximes against several clinical isolates of *Trypanosoma brucie*.

Methods: A series of 20 bisbenzamidines and bisbenzamidoximes were synthesized and tested in vitro against a drug-sensitive strain of *T. b. brucei* Lab 110 EATRO and a drugresistant strain of *T. b. r*. KETRI 243. The bisamidoximes were designed to improve oral bioavailability by functioning as orally-active prodrugs of the most active bisamidines. The in vivo efficacy of 8 bisbenzamidines and bisbenzamidoximes were evaluated using mice infected with the drug-sensitive (*T. b. brucei* Lab 110 EATRO) or drug-resistant strains of *T.b.r*. KETRI 2002 and KETRI 2538.

Results: The tested compounds generally showed similar in vitro potencies against both strains of *T.b*. The most potent compounds were bisbenzamidines linked with a hexanediamide, heptanediamide or octanediamide group (inhibitory concentration for 50% (IC50) = 1-3 nM). Several of the most potent bisbenzamidine compounds were effective in curing mice infected with the drug-sensitive or drug-resistant strains of *T. b. rhodesiense*. Curative doses were < 15 mg/kg/day for 3 days given by the intraperitoneal injection in the mouse model of infections. However, replacing the terminal basic bisamidines with less basic bisamidoxime groups resulted in prodrugs that were not orally effective against *T. b. brucei* infected mice.

Conclusion: The results suggest that alkanediamide-linked bisbenzamidines are highly effective against *T. brucei*, but further optimization of the prodrug strategy is needed to improve their oral bioavailability.

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A critical role of CD2 as an immunoprophylactic agent to combat visceral leishmaniasis

S. Sinha[1,*], S. Bimal[2], S. Sundaram[1]

[1] *Allahabad University, Allahabad, India*
[2] *Rajendra Memorial Research Institute for Medical Sciences, Patna, Bihar, India*

Background: A major Concern for VL prevention appears to be the inability of their CD4+ T cells to mount an adequate TH1 response which ensures the possible cure of the disease. Similarly the effectiveness of SAG in intact animal is determined by the host cell-mediated immune response. The present study aims at evaluating the use of CD2 antibody as an immunotherapeutic agent along with SAG in ensuring treatment of BALB/c mice induced with experimental Visceral leishmaniasis.

Methods: Mice were infected with *Leishmania donovani* promastigotes. Another set served as control. After seven week of infection, a set of mice from infected group was subjected to SAG treatment and another group was subjected to SAG treatment along with stimulation with antiCD2 antibody.CD4 cells expressing CD-25 were immunophenotyped and cytokines like IL-2, IFN-γ and TNF-α were assessed using FACS. We also looked into cell cycle pattern, expression of CD25+ cells on T cells, percentage of lymphocytes converted into lymphoblasts, percentage of activated T lymphocytes and IL-2 production. These parameters were evaluated in T cells both before and after stimulation of their CD2 antigen.

Results: We recorded a substantial enhancement of protective cytokines which are essential for combating visceral leishmaniasis infection.We also observed a significant reduction in parasitic load when drugs are used in combination with this immunoprophylactic agent

Conclusion: CD2 proved to be an important immunoprophylactic agent which if used in combination with drugs can provide a suitable and substantial cure against visceral leishmaniasis

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Patients with suspected visceral leishmaniasis in Istanbul

H. Cakan[1,*], S. Saribas[2], V. Oz[1], E. Polat[3], M. Aslan[2], B. Kocazeybek[3]

[1] *Istanbul University, Forensic Medicine Institue, Istanbul, Turkey*
[2] *Istanbul University, Cerrahpasa Faculty of Medicine, Istanbul, Turkey*
[3] *Istanbul University Cerrahpasa Faculty of Medicine, Turkey, Turkey*

Background: Visceral Leishmaniasis (VL) is a parasitic disease caused by *Leishmania infantum*. It is transmitted through bites of infected sand flies (female Phlebotomus). We aimed to investigate bone marrow and blood samples obtained from the patients with suspected VL.

Methods: Fifty-nine patients with suspected VL from Istanbul were included in this work. Bone marrow and blood samples of these patients were tested for possible VL