Type: Poster Presentation

Final Abstract Number: 45.044
Session: Parasitology and Parasitic Infections
Date: Thursday, April 3, 2014
Time: 12:45-14:15
Room: Ballroom

Modification of CYP2B6-mediated site of metabolism on Artemisinin molecule as a way to prolong its maximal antimalarial efficacy

I. Tsyrlov[1,*], C.S.T. Woo[2], V.P. Martin[2], I.N. Shur[3]

[1] *XENOTOX, Inc., Scarsdale, NY, USA*
[2] *XENOTOX, Inc., Scarsdale, USA*
[3] *ISI Medicine, Bronx, USA*

Background: A sesquiterpene endoperoxide lactone, artemisinin (AM), has become first-line natural antimalarial drug highly efficient in areas of multidrug resistance. The AM has a short half-life, and is being used with long acting blood schizontocidal drugs with different targets in the parasite. However, a combination therapy was linked to adverse drug interactions, and attributed to lower efficacy of AM. A unique 1,2,4-trioxane ring is essential for activity of the parent substrate, as all known AM metabolites were inactive due to the endoperoxide bridge was reduced to an epoxide. It was reaffirmed, both in vivo and in human liver microsomes that AM to be principally metabolized by CYP2B6 isozyme.

Methods & Materials: Previously, under similar circumstances of highly potent parent drugs, and the CYP2B6 demethylasing them into non-active products, we had developed site-directed modification of a substrate molecule by substituting its methyl groups with isopropyl groups. The latters create steric hindrance at CYP2B6 active site thus affecting ligand binding and lowering catalysis. Such strategy was applied in this study. While AM is biosynthesized in Artemisia annual plant extracts from mevalonic acid via dimethylallyl and isopentenyl pyrophosphates, here C-2 dimethylallyl groups at pyrophosphate were substituted with isopropylallyl groups. Isopropylartemisidin (IPAM) molecule appears to retain an intact 1,2,4-trioxane ring incorporating an endoperoxide bridge determined by a specific LC-MS/MS assay.

Results: The IPAM was incubated with human liver microsomes from eight different healthy donors, and concentration-time data were assessed by a first-order depletion model. With correlation to the metabolic rate constants for CYP2B6 probe substrates, efavirenz and bupropion, our data revealed that IPAM was metabolized by CYP2B6 at least 12-13 times slower than AM. Using procedure described by Robert et al. (2005), the hydroxylated and glucuronyl-conjugated derivatives of covalent heme adducts were determined in urine of *Plasmodium* infected mice by means of LC-MS. Namely, the amount of covalent heme-drug adducts was identically high in infected mice treated with 40 nM AM or 40 nM IPAM, compared to mice treated with 40 nM AM metabolites lacking trioxane ring endoperoxide bridge.

Conclusion: IPAM appears to represent a new potent antimalarial drug that can target multiple stages of the parasite's life cycle.

http://dx.doi.org/10.1016/j.ijid.2014.03.784

Type: Poster Presentation

Final Abstract Number: 46.001
Session: Travel Medicine and Travel Health
Date: Thursday, April 3, 2014
Time: 12:45-14:15
Room: Ballroom

Travel-associated Legionnaires' disease in European visitors to South Africa

J. Thomas[1,*], R. Stewart[2], A. Sanderson[3], A. Duse[2]

[1] *National Institute for Communicable Diseases, Johannesburg, South Africa*
[2] *National Health Laboratory Service, Johannesburg, South Africa*
[3] *Hydrosmart, Johannesburg, South Africa*

Background: Through a collaboration with the European Legionnaires' Disease Surveillance Network (ELDSNet), which is co-ordinated by the European Centre for Disease Prevention and Control, travel-associated Legionnaires' disease (TALD) cases with likely infection in South Africa are reported to a local team for further investigation.

Methods & Materials: All TALD cases reported by ELDSNet to the local team between January 2010 and November 2012 were retrospectively reviewed and analysed. All cases had stayed at or visited an accommodation site in South Africa during the disease incubation period (2-10 days prior to onset of illness).

Results: A total of 7 cases was identified: two single cases, a cluster of two cases and a complex cluster of 3 cases. The case-patients ranged in age from 48 – 88 years (median 65 years) and 4 were male; country of residence included the Netherlands (n = 4), United Kingdom (n = 2) and Norway (n = 1). All presented with pneumonia on return from travel to South Africa, and were confirmed LD based on urinary antigen testing. Outcome is known for 6 cases; 5 recovered and one died. The cluster was epidemiologically linked to a single accommodation site in Western Cape Province, while the complex cluster cases reported three common accommodation sites in two provinces (Western Cape and Eastern Cape). One of the single cases had stayed in both residential and holiday accommodation sites in KwaZulu-Natal, whilst the other reported staying at numerous accommodation sites in Western Cape, KwaZulu-Natal and Gauteng provinces. The cluster and complex cluster were investigated; a total of 8 accommodation sites underwent Legionella risk assessments and water sample testing. No sites had appropriate legionella monitoring and control programmes in place. High counts of *Legionella pneumophila* (LP) sg1 were detected in water samples from 2 sites, and of LP sg 2-14 at 4 sites. Common high-risk profile systems included domestic water distribution systems, evaporative condensers and spa pools.

Conclusion: TALD cases in European tourists visiting South Africa have occurred and will likely continue to be reported. There is a lack of awareness amongst South African accommodation sites with regards the need to institute legionella monitoring and control programmes.

http://dx.doi.org/10.1016/j.ijid.2014.03.785