Acta Tropica 185 (2018) 34–41

Contents lists available at ScienceDirect

Acta Tropica

journal homepage: www.elsevier.com/locate/actatropica

Emerging role of amiodarone and dronedarone, as antiarrhythmic drugs, in treatment of leishmaniasis

A. Oryan[a,*], E. Bemani[a], S. Bahrami[b]

[a] Department of Pathology, School of Veterinary Medicine, Shiraz University, Shiraz, Iran
[b] Department of Parasitology, Faculty of Veterinary Medicine, Shahid Chamran University of Ahvaz, Ahvaz, Iran

ARTICLE INFO

Keywords:
Amiodarone
Dronedarone
Leishmania spp.
Leishmaniasis

ABSTRACT

Leishmaniasis is a group of human and animal diseases causing 20,000–40,000 annual deaths and its etiological agents belong to the *Leishmania* genus. The most current treatment against leishmaniasis is chemotherapy. Pentavalent antimonials such as glucantime and pentostam have been administrated as the first-line drugs in treatment of various forms of leishmaniasis. The second-line drugs such as amphotericin B, liposomal amphotericin B, miltefosine, pentamidine, azole drugs and paromomycin are used in resistant cases to pentavalent antimonials. Because of drawbacks of the first-line and second-line drugs including adverse side effects on different organs, increasing resistance, high cost, need to hospitalization and long-term treatment, it is necessary to find an alternative drug for leishmaniasis treatment. Several investigations have reported the effectiveness of amiodarone, the most commonly used antiarrhythmic drug, against fungi, *Trypanosomes* and *Leishmania* spp. *in vitro*, *in vivo* and clinical conditions. Moreover, the beneficial effects of dronedarone, amiodarone analogues, against *Trypanosoma cruzi* and *Leishmania mexicana* have recently been demonstrated and such treatment regimens resulted in lower side effects. The anti- leishmanial and anti- trypanosomal effectiveness of amiodarone and dronedarone has been attributed to destabilization of intracellular Ca^{2+} homeostasis, inhibition of sterol biosynthesis and collapse of mitochondrial membrane potential. Because of relative low cost, excellent pharmacokinetic properties, easy accessibility and beneficial effects of amiodarone and dronedarone on leishmaniasis, they are proper candidates to replace the current drugs used in leishmaniasis treatment.

1. Introduction

Different species of the *Leishmania* (*L*) genus, the obligatory intracellular protozoa belonging to the family *Trypanosomatidae*, are the causative agent of a group of human and animal diseases that are termed leishmaniasis (Akbari et al., 2017; de Macedo-Silva et al., 2011; Oryan et al., 2008; Teixeira et al., 2013). These parasites exist in two forms with two hosts: extracellular motile flagellated promastigotes in the sandflies and intracellular aflagellated amastigotes in the mammalian hosts (Esch and Petersen, 2013; Oryan et al., 2008, 2007). At the moment, leishmaniasis, a major zoonotic disease, is endemic in large areas of the world including the Mediterranean basin and tropical and subtropical regions (Desjeux, 2004; Diniz et al., 2008; Oryan and Akbari, 2016). Because of several drawbacks of the current anti-lieshmanial compounds, failure to achieve a perfect cure and lack of a commercial and effective human vaccine (Akbari et al., 2017; Gupta et al., 2013; Savoia, 2015; Serrano-Martín et al., 2009a), there is an urgent need in development of new drugs that are efficacious, inexpensive, safe, less toxic, free of drug resistance, more accessible and easy to use without having to be hospitalized (Akbari et al., 2017; de Macedo-Silva et al., 2011; Oryan, 2015).

It has been shown that amiodarone, the most common antiarrhythmic drug used worldwide, is active against a lot of pathogenic fungi and protozoa especially several *Leishmania* species (de Macedo-Silva et al., 2011; Gupta et al., 2003; Serrano-Martín et al., 2009a). Furthermore, *in vitro* activity of dronedarone, an analogous of amiodarone, against *Trypanosoma* (*T*) *cruzi* and *L. mexicana* has recently been shown (Benaim et al., 2014, 2012). Amiodarone and dronedarone have excellent pharmacokinetics and can be the acceptable candidates as alternative drugs in treatment of leishmaniasis. The present article is a review of amiodarone and dronedarone properties, their anti-leishmanial activities, mechanisms of action, and possible methods to enhance the anti-leishmanial effects along with reducing the side effects of these therapeutic agents.

2. Leishmaniasis

Leishmaniasis is a critical public health problem worldwide

* Corresponding author.
E-mail address: oryan1215@gmail.com (A. Oryan).

https://doi.org/10.1016/j.actatropica.2018.04.022
Received 30 October 2017; Received in revised form 18 April 2018; Accepted 19 April 2018
Available online 22 April 2018
0001-706X/

(Serrano-Martín et al., 2009a) that frequently affects the poor people of developing countries (Akbari et al., 2017; Oryan, 2015; Savoia, 2015). Annually 20,000–40,000 deaths occur by leishmaniasis (Alvar et al., 2012; Esch and Petersen, 2013). At least 350 million people live in areas at risk for leishmaniasis and 14 million of them are affected by the disease (Oryan et al., 2008; Savoia, 2015) and its incidence is increasing because of environmental changes and individual risk factors (Desjeux, 2004; Oryan et al., 2014; Oryan and Akbari, 2016; Savoia, 2015).

2.1. Clinical manifestations

Approximately 21 species of *Leishmania* have been described to cause a broad spectrum of clinical diseases. Clinical appearances depend on the host-parasite interaction, species and genetic variation of the parasite, *Leishmania*/HIV co-infections, mixed infections with different *Leishmania* species and the immunological status of the host (de Macedo-Silva et al., 2011; de Medeiros et al., 2011; Esch and Petersen, 2013; Gupta et al., 2013; Oryan, 2015; Oryan et al., 2013b, 2008; Shirian et al., 2012). However, three different clinical manifestations, the cutaneous, mucocutaneous, and visceral leishmaniasis, are the most frequent forms (Akbari et al., 2017; Oryan, 2015; Teixeira et al., 2013). Cutaneous leishmaniasis (CL) may show various clinical manifestations of localized skin lesions such as papules, crusted nodules, plaques, or ulcerative nodular lesions which can heal within a few months but may become chronic, leading to severe tissue destruction and leave scars (Desjeux, 2004; Gupta et al., 2013; Oryan et al., 2013b, 2007; Shirian et al., 2014). Mucosal leismaniasis includes extensive destructive lesions mostly seen in mucous membrane of the nose but may involve the lips, mouth, pharynx, and larynx. Therefore, eating becomes difficult and risk of the secondary infections increases and can progress to malignant lesions (Daneshbod et al., 2011; Gupta et al., 2013; Oryan et al., 2013a; Shirian et al., 2012). Visceral leishmaniasis or kala-azar, the most severe form of leishmaniasis, is associated with clinical manifestations such as severe cachexia, long-term fever, fatigue, weakness, splenomegaly and hepatomegaly and can be fatal if not treated (Gupta et al., 2013; Oryan, 2015).

2.2. Diagnosis

There are different laboratory tests for diagnosis of leishmaniasis including:

- Giemsa/leishman staining of the smears taken from skin lesions, spleen, bone marrow and lymph node aspirates to observe amastigotes inside the macrophages (Alidadi and Oryan, 2014; Daneshbod et al., 2011; Khan et al., 2014; Mehrabani et al., 2011; Oryan et al., 2013a; Shirian et al., 2014).
- Inoculation of the aspirates into genetically susceptible animals to *Leishmania* such as BALB/c mice (Mehrabani et al., 2011).
- Culturing the aspirates (Khan et al., 2014; Mehrabani et al., 2011; Oryan et al., 2008).
- Application of serologic tests such as complement fixation test, direct agglutination test, enzyme-linked immunosorbent assay, and indirect immunofluorescent antibody test (Daneshbod et al., 2011; Oryan, 2015).
- Isoenzyme electrophoresis (Mehrabani et al., 2011).
- Histopathologic and ultrastructural examination (Mehrabani et al., 2011; Oryan et al., 2008; Shirian et al., 2012).
- Immunohistochemistry (Oryan et al., 2013a; Shirian et al., 2014)
- Molecular assays such as polymerase chain reaction (PCR) and nested-PCR assay (Abbasi et al., 2013; Khan et al., 2014; Mehrabani et al., 2011; Oryan et al., 2013a, 2013b; Shirian et al., 2012).

2.3. Current treatments and their problems

Methods of leishmaniasis treatment are different and depend on geographic regions, clinical manifestations, and *Leishmania* species (Alidadi and Oryan, 2014). Some of these methods are systemic treatments, surgical excision, cryotherapy, thermotherapy, laser therapy and use of ointment as topical treatments (Cardona-Arias et al., 2015; Jaffary et al., 2016; Oryan and Alemzadeh, 2016; Sundar and Chakravarty, 2015). However, chemotherapy as topical and systemic is still the most popular treatment against leishmaniasis (Bahrami et al., 2016; Serrano-Martín et al., 2009a). Pentavalent antimonials such as glucantime (meglumine antimoniate) and pentostam (sodium stibogluconate) are the first-line treatment for various forms of leishmaniasis. The second line treatments such as amphotericin B and its liposomal formulation, miltefosine, pentamidine, azole drugs and paromomycin are used in the resistant cases to pentavalent antimonials (Akbari et al., 2017; Alidadi and Oryan, 2014; de Macedo-Silva et al., 2011; Sundar et al., 2010). Furthermore, in recent years the plant-derived compounds and nano medicines have been used as valuable approaches in treatment of leishmaniasis (Akbari et al., 2017; Bahrami et al., 2015; Oryan, 2015; Oryan and Alemzadeh, 2016).

Limitations of glucantime and pentostam are the requirement for long course parenteral administration in order to obtain optimal outcomes, and this increases the parasite's resistance and results in pancreatic, renal and cardiac toxicity (Bahrami et al., 2016; Pandey et al., 2005; Serrano-Martín et al., 2009b). Amphotericin B is expensive and requires hospitalization because its IV infusion lasts six hours (Sinha et al., 2011). Liposomal amphotericin B also has high cost and needs hospitalization but it results in lower complications such as toxicity, prolonged course of parenteral therapy and development of drug resistance compared to amphotericin B (Akbari et al., 2017; Sundar et al., 2010). Despite the easy administration route of miltefosine (orally), teratogenic effects and the need to monitor the gastrointestinal side-effects have limited its use (de Macedo-Silva et al., 2011; Savoia, 2015; Serrano-Martín et al., 2009b). Pain at the injection site, reversible elevation of hepatic transaminases and ototoxicity may occur in treatment of paromomycin, and aminoglycoside antibiotics (Sundar and Chakravarty, 2015). The most important disadvantage of the nano-based carriers are difficult oral delivery, high price and cytotoxicity effects on macrophages (Jebali and Kazemi, 2013; Oryan and Alemzadeh, 2016).

3. Amiodarone

Amiodarone [2-butyl-3-(3′;5′ diiodo-4′α-diethyl-aminoethoxy-benzoyl)-benzofuran], was introduced as an anti-angina compound after its discovery by the chemists Tondeur and Binon at the Labaz, a Belgian company, in 1962 (Deltour et al., 1962; Eskes and Wiersinga, 2009; Halici et al., 2007; Pham et al., 2013) (Fig. 1). It was approved as a class III antiarrhythmic agent by FDA in United States in 1985 (Narayana et al., 2011; Pham et al., 2013). Nowadays, amiodarone is the most commonly used antiarrhythmic drug worldwide (Narayana et al., 2011). It is a multiple ion channel (Ca^{2+}, Na^{+}, K^{+}) blocker and a non-

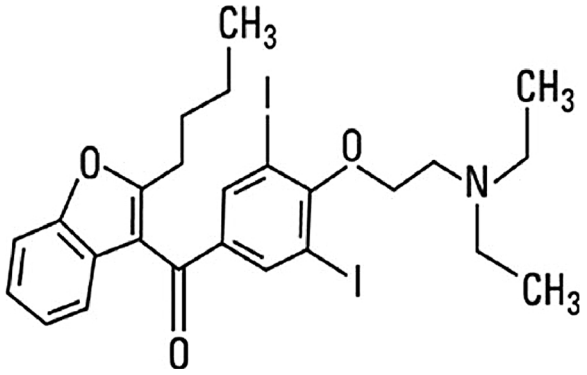

Fig. 1. Chemical structure of amiodarone.