Acta Tropica 126 (2013) 115–126

Contents lists available at SciVerse ScienceDirect

Acta Tropica

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

Review article

Advances with the Chinese anthelminthic drug tribendimidine in clinical trials and laboratory investigations

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ARTICLE INFO

Article history:
Received 4 June 2012
Received in revised form 8 January 2013
Accepted 11 January 2013
Available online 23 January 2013

Keywords:
Tribendimidine
Clinical trials
In vitro studies
In vivo studies
Chemotherapy
Pharmacokinetics
Nematode
Trematode
Cestode
Soil-transmitted helminthiases
People's Republic of China

ABSTRACT

The anthelminthic drug tribendimidine has been approved by Chinese authorities for human use in 2004, and a first comprehensive review was published in *Acta Tropica* in 2005. Here, we summarise further advances made through additional clinical trials and laboratory investigations. Two phase IV trials have been conducted in the People's Republic of China, the first one enrolling 1292 adolescents and adults aged 15–70 years and the second one conducted with 899 children aged 4–14 years who were infected with one or multiple species of soil-transmitted helminths. Oral tribendimidine (single 400 mg enteric-coated tablet given to adolescents/adults and 200 mg to children) showed high cure rates against *Ascaris lumbricoides* (90.1–95.0%) and moderate-to-high cure rates against hookworm (82.0–88.4%). Another trial done in school-aged children using a rigorous diagnostic approach found a cure rate against hookworm of 76.5%. A single oral dose of tribendimidine showed only low cure rates against *Trichuris trichiura* (23.9–36.8%) confirming previous results. Tribendimidine administered to children infected with *Enterobius vermicularis* (two doses of 200 mg each on consecutive days) resulted in a high cure rate (97.1%). Importantly, a series of randomised, exploratory trials revealed that tribendimidine shows interesting activity against the liver flukes *Opisthorchis viverrini* and *Clonorchis sinensis*, the tapeworm *Taenia* spp. and the threadworm *Strongyloides stercoralis* with respective cure rates of 70.0%, 40.0%, 53.3% and 36.4%. Pharmacokinetic studies in healthy Chinese volunteers indicated that after oral administration of tribendimidine, no parent drug was detected in plasma, but its primary metabolite, *p*-(1-dimethylamino ethylimino) aniline (aminoamidine, deacylated amidantel) (dADT), was found in plasma. dADT is then further metabolised to acetylated dADT (AdADT). dADT exhibits activity against several species of hookworm and *C. sinensis* in experimental studies, similar to that of tribendimidine. First studies elucidating the mechanism of action suggested that tribendimidine is an L-type nicotinic acetylcholine receptor agonist. Additional experimental studies revealed that the anti-parasite spectrum of tribendimidine is very broad. Indeed, to date, activity has been documented against 20 different nematode, trematode and cestode species. Taken together, tribendimidine warrants further scientific inquiry, including more comprehensive toxicity appraisals, mechanism of action studies and clinical investigation as it holds promise as a broad spectrum anthelminthics.

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http://dx.doi.org/10.1016/j.actatropica.2013.01.009

1. Introduction

Soil-transmitted helminthiases are parasitic worm infections caused by the roundworm *Ascaris lumbricoides*, the whipworm *Trichuris trichiura* and two species of hookworm, *Ancylostoma duodenale* and *Necator americanus* (Bethony et al., 2006; Knopp et al., 2012). More than 5 billion people are at risk of soil-transmitted helminthiases (Pullan and Brooker, 2012), with over a billion people currently infected with at least one, often two or all three main soil-transmitted helminth species (Bethony et al., 2006; Steinmann et al., 2010; Utzinger, 2012). Yet, soil-transmitted helminthiases have been tagged as neglected tropical diseases, as they are intimately linked with poverty and chiefly affect poor people in tropical and subtropical parts of the world (Hotez et al., 2007; Utzinger et al., 2012).

The current global strategy to control soil-transmitted helminthiases is preventive chemotherapy, which refers to the regular large-scale administration of anthelminthic drugs to entire at-risk populations, especially school-aged children (WHO, 2006, 2010). At present, the World Health Organization (WHO) features four anthelminthic drugs on their model list of essential medicines for the treatment of soil-transmitted helminth infection, albendazole, levamisole, mebendazole and pyrantel pamoate (WHO, 2011a). Albendazole and mebendazole are the most widely used anthelminthics with dozen of millions of people treated every year (WHO, 2011b). However, these four drugs have all been developed in the 1960s and 1970s, initially for the veterinary market, and hence they lack optimisation for human use (Geary et al., 2010; Keiser and Utzinger, 2010; Olliaro et al., 2011). Moreover, there is considerable concern that growing drug pressure might result in the development of resistant parasite strains. Indeed, several recent studies carried out in different epidemiological settings reported unexpectedly low cure rates after single-dose albendazole or mebendazole administrations against hookworm and *T. trichiura* in school-aged children (Albonico et al., 2003; Flohr et al., 2007; Knopp et al., 2010; Steinmann et al., 2011; Ayé Soukhathammavong et al., 2012). A systematic review and meta-analysis concluded that a single dose of albendazole or mebendazole shows high efficacy against *A. lumbricoides* infection, poor efficacy against *T. trichiura* infection, whereas albendazole is more efficacious than mebendazole against hookworm infection (Keiser and Utzinger, 2008). In view of these observations, along with global policies and experiences from veterinary public health (Geerts and Gryseels, 2000; Horton, 2003), there is a need to develop new anthelminthic drugs, ideally with different mechanisms of action than the current armamentarium (Hagel and Giusti, 2010; Keiser and Utzinger, 2010; Olliaro et al., 2011).

Towards the end of the 1970s, a new class of chemical compounds of aminophenylamidines was reported to have a broad spectrum of activity against intestinal nematodes, filariae and cestodes. In particular, amidantel (ADT, BAY d 8815; Fig. 1a) showed high efficacy against hookworm and large roundworm harboured in dogs (Thomas, 1979; Wollweber et al., 1979). In 1980, a first clinical study in man indicated that amidantel is highly efficacious against *A. lumbricoides* and *A. duodenale*, whereas only few patients infected with *N. americanus* were cured (Rim et al., 1980). In 1983, Chinese scientists synthesised amidantel and its derivatives and pursued detailed structure-activity relationship studies. Eventually, tribendimidine (Fig. 1b) was selected and this compound further progressed in the drug development pipeline (Yao and Chen, 1986). After many years of scientific inquiry, including detailed pre-clinical and clinical studies, in early 2004, tribendimidine was approved by the Chinese Food and Drug Administration for the treatment of soil-transmitted helminth infections in man. In the following year, we published a review in *Acta Tropica* that summarised – for the first time – the pharmacological, toxicological, laboratory and clinical data available at the time (Xiao et al., 2005). Key characteristics of tribendimidine were highlighted, namely its good safety profile and the high efficacy against *A. lumbricoides*. Although tribendimidine only showed low efficacy against *T. trichiura*, it was found that a single dose of tribendimidine shows equal or even higher efficacy against hookworm (particularly *N. americanus*, which is the dominant hookworm species in the People's Republic of China (P.R. China)) than albendazole or other anthelminthics currently in use.

Here, we review advances made with tribendimidine over the past 8 years. First, we summarise results from recent clinical trials done in P.R. China, including two phase IV trials against soil-transmitted helminth infection in children and adolescents/adults. Next, we highlight key findings from a series of randomised, exploratory trials focussing on other helminth infections (clonorchiasis, opisthorchiasis, strongyloidiasis and taeniasis). Moreover, we provide an update on pharmacokinetic investigations and first insights gained from mechanism of action studies. We summarise the latest laboratory investigations, emphasising the wide spectrum of activity of tribendimidine against a broad array of nematode, trematode and cestode species. Our review is concluded with an outlook and a perspective of open research needs.

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