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Off-target effects of tribendimidine, tribendimidine plus ivermectin, tribendimidine plus oxantel-pamoate, and albendazole plus oxantel-pamoate on the human gut microbiota

Pierre H.H. Schneeberger[a,b,*], Jean T. Coulibaly[a,b,d,e], Morgan Gueuning[c], Wendelin Moser[a,b], Bryan Coburn[f,g], Jürg E. Frey[c], Jennifer Keiser[a,b]

[a] Department of Medical Parasitology and Infection Biology, Swiss Tropical and Public Health Institute, Basel, Switzerland
[b] University of Basel, Basel, Switzerland
[c] Agroscope, Department of Method Development and Analytics, Research Group Molecular Diagnostics, Genomics and Bioinformatics, Wädenswil, Switzerland
[d] Unité de Formation et de Recherche Biosciences, Université Felix Houphouët-Boigny, Abidjan, Cote d'Ivoire
[e] Centre Suisse de Recherches Scientifiques en Côte d'Ivoire, Abidjan, Cote d'Ivoire
[f] Departments of Medicine and Laboratory Medicine & Pathobiology, University of Toronto, Toronto, Canada
[g] Department of Medicine, Division of Infectious Diseases, University Health Network, Toronto, Canada

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ABSTRACT

Soil-transmitted helminths infect 1.5 billion people worldwide. Treatment with anthelminthics is the key intervention but interactions between anthelminthic agents and the gut microbiota have not yet been studied. In this study, the effects of four anthelminthic drugs and combinations (tribendimidine, tribendimidine plus ivermectin, tribendimidine plus oxantel-pamoate, and albendazole plus oxantel-pamoate) on the gut microbiota were assessed. From each hookworm infected adolescent, one stool sample was collected prior to treatment, 24 h post-treatment and 3 weeks post-treatment, and a total of 144 stool samples were analyzed. The gut bacterial composition was analyzed using 16S rRNA gene sequencing. Tribendimidine given alone or together with oxantel-pamoate, and the combination of albendazole and oxantel pamoate were not associated with any major changes in the taxonomic composition of the gut microbiota in this population, at both the short-term post-treatment (24 h) and long-term post-treatment (3 weeks) periods. A high abundance of the bacterial phylum *Bacteroidetes* was observed following administration of tribendimidine plus ivermectin 24 h after treatment, due predominantly to difference in abundance of the families *Prevotellaceae* and *Candidatus homeothermaceae*. This effect is transient and disappears three weeks after treatment. Higher abundance of *Bacteroidetes* predicts an increase in metabolic pathways involved in the synthesis of B vitamins. This study highlights a strong relationship between tribendimidine and ivermectin administration and the gut microbiota and additional studies assessing the functional aspects as well as potential health-associated outcomes of these interactions are required.

1. Introduction

Recent estimates suggest that the worldwide prevalence of soil-transmitted helminths (STHs), including infection with *Ascaris lumbricoides*, *Trichuria trichuris* and hookworm, is 1.5 billion people (Hotez et al., 2009; Pullan et al., 2014; Jourdan et al., 2017). The total estimated burden due to STHs is 3.4 million disability-adjusted life years (GBD, 2015 DALYs and HALE Collaborators, 2016). The symptoms associated with STH infection are not specific and are usually more severe and debilitating in school-aged children and in the elderly. Children who are chronically infected can display malnutrition and developmental delay while elderly people infected with STHs often display reduced work-related productivity (Bethony et al., 2006).

Four drugs (albendazole, mebendazole, pyrantel pamoate, levamisole) are on the World Health Organization's list of essential medicines for the treatment of STH infections (WHO, 2002). The two benzimidazoles (albendazole and mebendazole) are most commonly used drugs in preventive chemotherapy programs (WHO, 2002; Keiser and Utzinger, 2008; Abou-Zeid et al., 2012). Ivermectin has a broad spectrum of activity against different parasites ranging from nematodes

* Corresponding author. Department of Medicine, University Health Network, Toronto, ON, M5G 1L7, Canada.
E-mail address: pierre.schneeberger@utoronto.ca (P.H.H. Schneeberger).

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Table 1
Summary of volunteers investigated in this study. From each adolescent of each of the four treatments, a sample was collected before, 24 h after and 3 weeks after treatment. EPG = Hookworm eggs per gram of stool, FU = follow-up.

ID	Samples	EPG (baseline)	EPG (FU)	ID	Samples	EPG (baseline)	EPG (FU)
Treatment arm 1				**Treatment arm 2**			
P- 5	D6, E6, F6	318	426	P- 6	D8, E7, F7	144	0
P- 7	D9, E8, F8	30	0	P- 17	D21, E18, F18	12	0
P- 9	D11, E10, F10	96	132	P- 19	D23, E20, F20	84	0
P- 10	D12, E11, F11	36	228	P- 23	D27, E24, F24	1002	0
P- 11	D13, E12, F12	198	108	P- 27	D31, E28, F28	72	0
P- 14	D16, E15, F15	78	0	P- 33	D42, E30, F30	534	0
P- 22	D26, E23, F23	450	78	P- 34	D43, E31, F31	78	0
P- 26	D30, E27, F27	36	0	P- 35	D44, E44, F44	42	0
P- 29	D34, E40, F40	102	6	P- 43	D78, E45, F45	30	0
P- 32	D39, E43, F43	336	54	P- 46	D91, E37, F37	18	0
P- 38	D55, E33, F33	78	0	P- 48	D95, E34, F34	4740	0
P- 41	D76, E38, F38	240	0				
Treatment arm 3				**Treatment arm 4**			
P- 2	D3, E3, F3	450	66	P- 1	D1, E1, F1	42	36
P- 3	D4, E4, F4	966	0	P- 4	D5, E5, F5	96	288
P- 8	D10, E9, F9	186	210	P- 15	D18, E16, F16	534	0
P- 12	D14, E13, F13	126	0	P- 20	D24, E21, F21	66	0
P- 13	D15, E14, F14	492	108	P- 21	D25, E22, F22	204	90
P- 16	D20, E17, F17	630	516	P- 24	D28, E25, F25	426	24
P- 18	D22, E19, F19	696	282	P- 25	D29, E26, F26	72	108
P- 28	D33, E29, F29	1824	0	P- 31	D37, E41, F41	222	204
P- 30	D35, E42, F42	1698	1302	P- 37	D52, E46, F46	258	48
P- 36	D50, E47, F47	222	24	P- 40	D62, E36, F36	912	0
P- 39	D58, E48, F48	60	12	P- 42	D77, E39, F39	582	0
P- 44	D79, E2, F2	270	0	P- 47	D94, E32, F32	2580	60
P- 45	D86, E35, F35	168	0				

such as *Strongyloides stercoralis* or *A. lumbricoides* to filarial parasites, and arthropods and even affects the Anopheline vectors of malaria (Marti et al., 1996; Wen et al., 2008; Grayson et al., 2010; Ōmura and Crump, 2017). Oxantel has high activity against *T. trichuris* (Zaman and Sabapathy, 1975; Horton, 2003; Speich et al., 2014). Finally, tribendimidine has been shown to have a similar spectrum to that of albendazole, and could be an alternative to the latter in case of emergence of benzimidazole resistance (Xiao et al., 2013). There is growing consensus to use these drugs in combination to increase efficacy and decrease the risk of drug resistance.

Recent advancements in high-throughput sequencing technologies enable the characterization of the human microbiome (Turnbaugh et al., 2007; Arumugam et al., 2011; Human Microbiome Project Consortium, 2012), which was not possible at the time those drugs were introduced. Thus, the interactions of these anthelminthic drugs and drug combinations with the human gut microbiota composed of a variety of microorganisms, including other eukaryotic parasites, protozoa, viruses, fungi and most importantly bacteria (Nicholson et al., 2005; Lozupone et al., 2012; Schneeberger et al., 2016), can now be studied. Drug-microbiota interactions can modulate the bioavailability and activity of drugs and hence modulate their efficacy (Nicholson et al., 2005; Clayton et al., 2009; Wilson and Nicholson, 2009; Cheng et al., 2013; Maurice et al., 2013). STHs share the same environmental niche as the gut bacterial microbiota, but potential interactions between the gut microbiota and anthelminthic agents have not been assessed to date. The aim of this study was to identify potential interactions between these treatments and the non-target microbiota.

2. Methods

2.1. Sample collection and ethics statement

Samples were collected in the framework of a randomized, controlled, single blind, non-inferiority trial in the Agboville district in Côte d'Ivoire. Hookworm positive adolescents (age 15 to 18), confirmed by quadruplicate Kato-Katz thick smears, were randomly assigned to four treatment arms, including tribendimidine (400 mg), tribendimidine (400 mg) plus ivermectin (200 µg/kg), tribendimidine (400 mg) plus oxantel pamoate (25 mg/kg) and albendazole (400 mg) plus oxantel pamoate (25 mg/kg). Details about the study are presented elsewhere (Moser et al., 2017). From each adolescent, one stool sample was collected prior to treatment, 24 h post-treatment and 3 weeks post-treatment, and a total of 144 stool samples were analyzed (Table 1).

Ethical approval was obtained from the Comité National d'Ethique et de la Recherche in Côte d'Ivoire (083/MSHP/CNER-kp) and the Ethics Committee of North-western and Central Switzerland (EKNZ UBE-15/35). The trial was registered with ISRCTN (number 14373201).

2.2. Sample collection

For DNA isolation, 150–250 mg of stool sample was diluted in 500 µl of AVL buffer (Qiagen, Darmstadt, Germany) and subsequently homogenized using a soil-grinding SK38 kit on the Precellys 24 system (Bertin Technologies, Saint-Quentin, France). Homogenized samples were further extracted on a Magna Pure 96 system (Roche, Basel, Switzerland) using the DNA and Viral NA Large Volume kit (Roche, Basel, Switzerland) according to the manufacturers' protocol.

2.3. 16S amplicon PCR

2.5 µl of isolated DNA was used to perform amplification of the V3-V4 region using the following primer pair:

Forward primer = 5′-TCGTCGGCAGCGTCAGATGTGTATAAGAGACAGCCTACGGGNGGCWGCAG
Reverse primer = 5′-GTCTCGTGGGCTCGGAGATGTGTATAAGAGACAGGACTACHVGGGTATCTAATCC

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