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REVIEW ARTICLE

Systemic and Target-Site Pharmacokinetics of Antiparasitic Agents

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Abstract

About one-sixth of the world's population is affected by a neglected tropical disease as defined by the World Health Organization and Center for Disease Control. Parasitic diseases comprise most of the neglected tropical disease list and they are causing enormous amounts of disability, morbidity, mortality, and healthcare costs worldwide. The burden of disease of the top five parasitic diseases has been estimated to amount to a total 23 million disability-adjusted life-years. Despite the massive health and economic impact, most drugs currently used for the treatment of parasitic diseases have been developed decades ago and insufficient novel drugs are being developed. The current review provides a compilation of the systemic and target-site pharmacokinetics of established antiparasitic drugs. Knowledge of the pharmacokinetic profile of drugs allows for the examination and possibly optimization of existing dosing schemes. Many symptoms of parasitic diseases are caused by parasites residing in different host tissues. Penetration of the antiparasitic drug into these tissues, the target site of infection, is a prerequisite for a successful treatment of the disease. Therefore, for the examination and improvement of established dosing regimens, not only the plasma but also the tissue pharmacokinetics of the drug have to be considered. For the current paper, almost 7000 scientific articles were identified and screened from which 429 were reviewed in detail and 100 were included in this paper. Systemic pharmacokinetics are available for most antiparasitic drugs but in many cases, not for all the relevant patient populations and only for single- or multiple-dose administration. Systemic pharmacokinetic data in patients with organ impairment and target-site pharmacokinetic data for relevant tissues and body fluids are mostly lacking. To improve the treatment of patients with parasitic diseases, research in these areas is urgently needed.

Key Points

Most available antiparasitic drugs were developed decades ago and novel antiparasitic agents are urgently needed

Tissue pharmacokinetic studies for most antiparasitic drugs are lacking, but they are essential to optimize the treatment of parasitic diseases and we encourage scientists to help fill this gap

There also is a void of studies investigating the pharmacokinetic/pharmacodynamic relationship of antiparasitic agents. Extending the knowledge in this field will improve the treatment of patients infected with parasitic diseases worldwide

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1 Introduction

Parasitic diseases are responsible for a tremendous amount of disability, morbidity, mortality, and healthcare costs worldwide. About one-sixth of the world's population is infected with a neglected tropical disease (NTD) [1]. Although the NTDs as defined by the World Health Organization and Center for Disease Control are not exclusively made up by parasitic diseases, parasitic diseases comprise most of the NTD list. The Global Burden of Diseases Study from 2010 estimates the burden of disease of the top five parasitic diseases (cryptosporidiosis, intestinal nematode infections, leishmaniasis, schistosomiasis, and lymphatic filariasis) to amount to a total 22.94 million disability-adjusted life-years [2, 3]. Including other parasitic diseases from the group of NTDs, the number adds up to almost 30 million disability-adjusted life-years. This means that 30 million years of healthy life were lost to premature death and disability because of parasitic diseases. Although many parasitic diseases do not directly lead to death, still 248,900 yearly deaths due to parasitic diseases (excluding malaria) are estimated by the authors of the Global Burden of Disease Study [3].

Most of the parasitic infections are limited to developing countries in the tropics and subtropics and affect the world's poorest people. For a long time, pharmaceutical companies and industrial nations did not show much interest in developing new antiparasitic drugs and most drugs that are currently used for the treatment of these infections have been developed decades ago. In recent years, major efforts have been made by numerous organizations and initiatives to repurpose old drugs, develop new drugs, and improve the treatment of patients with parasitic disease worldwide.

In many parasitic diseases, the parasite invades certain tissues of the host, causing a variety of different symptoms. For the treatment of these infections, the antiparasitic drug has to reach the target site of the infection, the respective tissue. Therefore, for most parasitic infections, tissue penetration of the antiparasitic drugs is essential for clinical success of the treatment. Pharmacokinetic studies investigating the tissue pharmacokinetics of drugs can be employed to examine and potentially improve existing dosing schedules. This can increase the efficacy of the treatment and decrease the occurrence of drug toxicity. Furthermore, for repurposing of drugs, knowledge of their target-site penetration may be considered as a basis for exploring novel indications. With this review, we aim to accumulate the currently published data on the plasma pharmacokinetics and tissue pharmacokinetics of the globally available antiparasitic drugs.

2 Methods

A systematic search for human pharmacokinetic (PK) studies on anti-parasitic drugs in the PubMed US National Library of Medicine database was performed. Antimalarial drugs were excluded from this review because for most of these agents tissue penetration is not relevant and inclusion of all antimalarial drugs would be beyond the scope of this study. Animal tissue PK data are sometimes used to estimate the missing human tissue PK data. However, non-clinical PK data were not included in this review because the transfer of these data to humans has not been investigated thoroughly and could potentially mislead the clinically oriented reader.

Pharmacokinetic studies up to August 2019 were included in this review. The following search terms were used for each individual drug: "drug name" AND pharmacokinetics; "drug name" AND concentrations; "drug name" AND tissue.

A total number of 6904 studies were screened for relevant PK content with the use of the title and abstract (Fig. 1). If studies with potential PK data were identified, these were read in detail and PK parameters were gathered. In this review, only those studies that most accurately display the common dosing schedules and provide the most detail regarding plasma and tissue pharmacokinetics were included. The literature search was limited to publications in English and German. Studies on patients were only included if the study drug was administered for the treatment of a parasitic disease. Only original papers on human subjects were included. Pharmacokinetic studies on children were only included if no comparable study was identified in adults or if children constitute the main treatment population for the respective disease. Studies were excluded if another study in the same compartment and with the same or a very similar dosing schedule was available with a better quality of data or more patients studied.

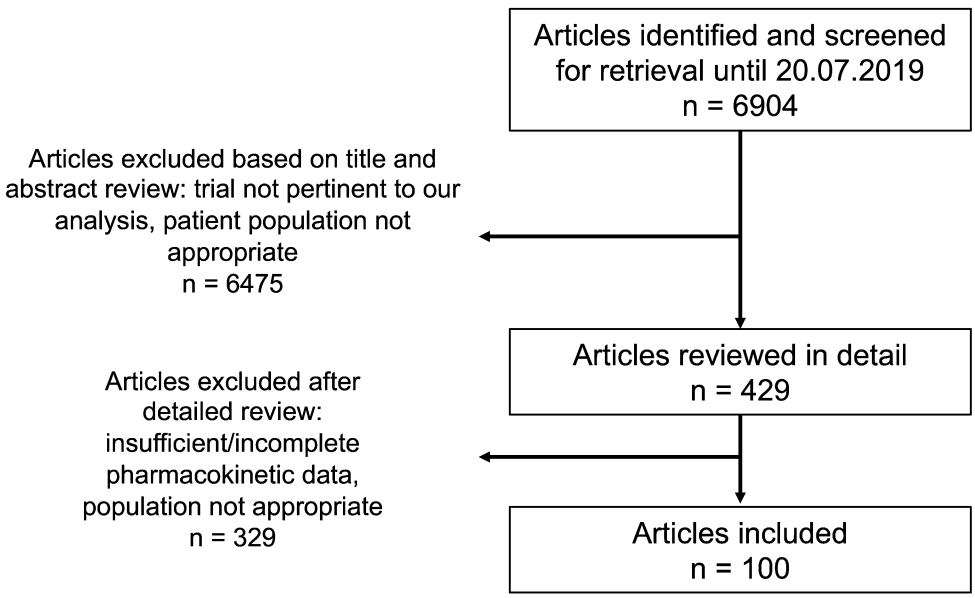

Fig. 1 Flowchart depicting reviewing and inclusion criteria and the number of articles reviewed

3 Systemic and Target-Site Pharmacokinetics

3.1 Albendazole

The PK parameters of albendazole (ALB) after oral administration of a single dose (SD) and multiple doses (MD) in healthy volunteers and patients are shown in Table 1. Studies were included only where ALB was ingested with food because administration with meals is recommended. As a result of the high lipid solubility and low aqueous solubility of ALB, high-fat foods substantially increase absorption of ALB [4]. In a study that investigated the effect of food intake on the absorption of ALB, a fatty meal led to a four-fold increase of the mean plasma area under the concentration–time curve (AUC) [5]. Albendazole is metabolized via a first-pass mechanism in the liver to the active compound ALB sulfoxide. Albendazole is only available for oral administration and the most commonly used dose is 400 mg daily. One study with diethylcarbamazine as concomitant medication was also included because this combination is indicated for certain parasitic diseases.

Albendazole can be used for the treatment of a variety of parasitic diseases. Among them loiasis, filariasis, giardiasis, cysticercosis, toxocariasis, echinococcosis, and soil-transmitted helminthiases. Therefore, the penetration of ALB into numerous target tissues is of relevance. Tissue PK studies for cerebrospinal fluid (CSF), breast milk, and echinococcal cyst fluid were included. Several other studies on the tissue pharmacokinetics of ALB have been published, but those were excluded from the review because of the poor quality of the data (no transfer ratios, only single concentrations measured, no PK calculations).

3.2 Amphotericin B

Amphotericin B (AmB) is available as a standard formulation with desoxycholate (AmBD) and two lipid formulations, namely AmB lipid complex (ABLC) and liposomal AmB (LAmB). The lipid formulations have been developed to decrease the nephrotoxic effects of AmBD. All three formulations can only be administered intravenously. Single-dose PK parameters of the three formulations are shown in Table 1, for ABLC, multiple-dose PK parameters are also given.

Therapeutic indications include systemic mycoses and infections with different protozoan pathogens, the most important being visceral leishmaniasis. Tissue penetration studies of AmB have been included in Table 2 for the following compartments: epithelial lung fluid, lung tissue, buccal mucosal tissue, and wound eschar. Two studies on tissue penetration of LAmB into pleural fluid are available in the literature, but they included only one patient each and were therefore not included in our table. The first study found a LAmB penetration ratio of 0.094 by dividing the AUC after 24 h in tissue by the AUC after 24 h in plasma. In this study, a patient with pulmonary zygomycosis and empyema was administered multiple doses of 7.5 mg/kg bodyweight LAmB every second day [6]. In the second study, a patient with sepsis and pneumonia showed a penetration ratio of 0.045 for LAmB. This ratio was calculated by dividing the concentration of LAmB in pleural effusion by the simultaneously measured concentration in plasma [7]. The same study also investigated penetration ratios of ABLC and ABCD into pleural effusion. For ABCD, five patients were analyzed and a mean ratio of 0.13 was found. The study included only one patient with ABLC with a penetration ratio of 0.45. Because this study does not include the exact dosing schedules and for LAmB and ABLC only one patient was studied, it was not included in Table 2 [7].

Only one study was identified in patients with organ impairment. This study is not shown in Table 3 because it was conducted in patients with continuous venovenous hemodiafiltration. The authors of this study report a half-life of 48.2 h, a clearance of 31 L/h, and a volume of distribution of 1607 L after a dose of 5 mg/kg bodyweight of ABLC [8].

3.3 Benznidazole

Benznidazole (BZD) belongs to the group of nitroimidazole anti-parasitic agents and is mainly used for the treatment of Chagas disease, an infection with *Trypanosoma cruzi*.

It is only available as an oral formulation and the usual dose is 5–10 mg/kg bodyweight per day in two divided doses. Detailed PK data after multiple doses have not been published; therefore, only SD PK data are provided in Table 1.

Trypanosoma cruzi can penetrate the central and peripheral nervous system and smooth muscle in the heart, oesophagus, and colon. However, thorough studies on tissue pharmacokinetics could not be identified, except for one penetration study into breast milk (Table 2).

3.4 Diethylcarbamazine

Diethylcarbamazine (DEC) is available as an oral and intravenous formulation; however, currently, only oral use is recommended. Oral doses from 2 to 6 mg/kg bodyweight are usually used. Data of two SD PK studies in healthy volunteers are provided in Table 1. Two studies investigating the plasma pharmacokinetics of DEC in patients with moderate and severe renal impairment could be identified (Table 3).

Table 1 Plasma pharmacokinetics of different antiparasitic drugs after single-dose (SD) and multiple-dose (MD) administration

Name	Dose			*N*	Health status	C_{max} (μg/mL)	$AUC_{(0-\infty)}$ (μg h/mL)	$AUC_{(0-24)}$ (μg h/mL)	$t_{1/2}$ (h)	Cl (L/h)	*V* (L)	References
Albendazole sulfoxide	Oral	400 mg	SD	14	HV	0.58 (0.53–0.68)	7.46 (6.61–10.17)	6.83 (6.05–9.49)[t]	10.2 (7.1–12.3)	48.7 (38.0–80.0)	740 (560–906)	[28]
Albendazole sulfoxide	Oral	400 mg	SD	14	HV	0.57 (0.51–0.71)	7.22 (6.48–9.78)	6.63 (5.95–9.12)[t]	10.3 (7–13.5)	44.4 (35.2–105.1)	712 (542–1064)	[28]
Albendazole sulfoxide	Oral	400 mg	SD	12	Bancroftian Filariasis	0.14 ± 0.051	2.54 ± 0.04	2.32 ± 0.048[t]	11.8 ± 33.9	83.5 ± 63.5	1420 ± 37	[29]
Albendazole sulfoxide	Oral	15 mg/kg/d	SD	16	Neurocysticercosis	0.1	1.11		4.4			[30]
Albendazole sulfoxide	Oral	15 mg/kg/d	bid, MD	16	Neurocysticercosis	0.43		2.97[tw]	6.1			[30]
Amphotericin B deoxycholate	i.v.	0.6 mg/kg BW	SD	5	HV	1.43 ± 0.2	46.6 ± 7.2	13.9 ± 2.0	127 ± 30	0.98 ± 0.15[c]	176 ± 15[c]	[31]
Liposomal amphotericin B	i.v.	1 mg/kg BW	SD	6	Peripheral stem cell transplant	8.1 ± 4.2	112.2 ± 75.3		9.7 ± 3.1	1.2 ± 0.83[c]	14.25 ± 10.5[c]	[32]
Liposomal amphotericin B	i.v.	1 mg/kg BW	od, MD on d7	6	Peripheral stem cell transplant patients	13.5 ± 9.1	333.7 ± 548.3		13 ± 11.8	0.83 ± 0.83[c]	12 ± 15[c]	[32]
Liposomal amphotericin B, radiolabeled	i.v.	2 mg/kg BW	SD	5	HV	22.9 ± 10	288 ± 209	171 ± 126	152 ± 116	7.28 ± 4.05[c]	122 ± 66[c]	[31]
Liposomal amphotericin B	i.v.	10 mg/kg/d	SD	7	Fungal infection	120 ± 70	1188 ± 1058	1062 ± 971	8 ± 1.5	1.35 ± 1.43[c]	17.25 ± 18[c]	[33]
Amphotericin B lipid complex	i.v.	5 mg/kg BW	SD	6	Critically ill	0.47	19.3		43	47.3		[8]
Amphotericin B lipid complex	i.v.	2.5 mg/kg BW	od, MD on d7	3	Hepatosplenic candidiasis	2.05 ± 0.55		15.3 ± 3.8		16.35 ± 3.53[c]		[34]
Benznidazole	Oral	100 mg	SD	8	HV	2.2 (2.8–1.7)	48.4 (57.2–40.9)		12.1 (13.7–11.1)	2.07 (2.4–1.7)	34.5 (39.7–29.5)	[35]
Diethylcarbamazine	Oral	150 mg	SD	12	HV	0.5 ± 0.23	5.84 ± 1.92		14.63 ± 6.72	2299 ± 1426[c]	42,750 ± 16,875[c]	[36]
Diethylcarbamazine	Oral	6 mg/kg BW	SD	14	HV	1.93 (1.81–2.09)	25.64 (23.35–29.67)	23.85 (21.65–29.09)[t]	9.0 (7.6–10.2)	14.5 (10.9–17.6)	182 (141–205)	[28]

Table 1 (continued)

Name	Dose			*N*	Health status	C_{max} (µg/mL)	$AUC_{(0-\infty)}$ (µg h/mL)	$AUC_{(0-24)}$ (µg h/mL)	$t_{1/2}$ (h)	Cl (L/h)	*V* (L)	References
Eflornithine	Oral	100 mg/kg BW	q6h, for 14d	12	Late-stage African trypanosomiasis	484 (296–598)*	4430 (2911–6420)**		10.6 (3.6–16.3)	7.5 (4.5–11.3)[c]	105 (51.8–200)[c]	[37]
Fexinidazole	Oral	1200 mg	SD	12	HV	1.79 (CV% 29)	21.47 (CV% 15)		11 (34)			[38]
Fexinidazole	Oral	1200 mg	SD	6	HV	0.27 (CV% 45)		2.44 (CV% 48)				[38]
Fexinidazole	Oral	1200 mg	od, MD on d14	6	HV	0.39 (CV% 39)		4.77 (CV% 54)				[38]
Ivermectin	Oral	150 mg	SD	10	HV	0.068 ± 0.048		0.77 ± 0.56[t]				[39]
Ivermectin	Oral	200 mg	SD	54	HV	0.043 ± 0.018	1.09 ± 0.51		80.7 ± 33.3	17.3 ± 9.2	1822 ± 857	[40]
Ivermectin	Oral	400 mg	SD	23	HV	0.05 (0.032–0.062)	1.36 (0.71–1.92)	1.34 (0.71–1.88)[t]	23.8 (17.4–33.2)		405 (285–758)[c]	[41]
Ivermectin	Oral	150 mg	SD	9	Onchocerciasis	0.038 ± 0.006		1.55 ± 0.19[un]	56.5 ± 7.5		743 ± 200[c]	[42]
Mebendazole	Oral	50 mg	SD	6	HV	0.037 ± 0.0068	0.53 ± 0.086		8.2 ± 2.9			[43]
Mebendazole	Oral	1000 mg	SD	8	HV	0.031 ± 0.026		0.21 ± 0.16	7.4 ± 2.2			[44]
Mebendazole	Oral	10 mg/kg BW	SD	5	Cystic hyatid disease	0.07 ± 0.04	0.28 ± 0.21	0.21 ± 0.17[t]	3.6 ± 0.7[a]			[45]
Mebendazole	Oral	10 mg/kg BW	q6h, MD	7	Cystic hyatid disease	0.14 ± 0.041		0.65 ± 0.24[t]	5.5 ± 2.05			[45]
Meglumine antimonate	i.m.	20 mg/kg BW	od, MD on d20	9	Cutaneous leishmaniasis	38.8 ± 2.1		190 ± 10	20.6 ± 1.8	7.95 ± 4.5[c]	22.5 ± 0.75[c]	[46]
Melarsoprol	i.v.	Treatment schedule according to national treatment guidelines of East Africa	MD	9	African trypanosomiasis	5303		21.21[un]	42.9	4.64[c]	261[c]	[47]
Metronidazole	i.v.	500 mg	SD	9	HV		151 ± 42		7.3 ± 1.0		36 ± 7.9	[48]
Metronidazole	Oral	500 mg	SD	9	HV		159 ± 48		7 ± 1.1		34 ± 8.2	[48]
Metronidazole	Oral	750 mg	SD	13	HV	11.3 ± 2.06	210 ± 45.7			0.063 ± 0.016	46.9 ± 14.6[c]	[49]
Metronidazole	Oral	400 mg	SD	6	HV	8.8 ± 1.3	121 ± 9.9		8 ± 1.11			[50]
Metronidazole	Oral	400 mg	bid, MD	6	HV	15.2 ± 2.8		128 ± 9.9[tw]	7.1 ± 1			[50]
Metronidazole	Oral	500 mg	SD	6	Schistosomiasis			129 ± 18	8.4 ± 1.3	5.48 ± 0.68[c]	59.3 ± 3.75[c]	[51]
Miltefosine	Oral	2.5 mg/kg/d	MD	30	Cutaneous leishmaniasis		36.7 (17.8–50.3)		34.4 (9.5–46.2)[d]			[52]

Table 1 (continued)

Name	Dose			*N*	Health status	C_{max} (µg/mL)	$AUC_{(0-\infty)}$ (µg h/mL)	$AUC_{(0-24)}$ (µg h/mL)	$t_{1/2}$ (h)	Cl (L/h)	*V* (L)	References
Moxidectin	Oral	8 mg	SD	27	HV	0.059 ± 0.013	3.39 ± 1.32		784 ± 347	2.76 ± 1.28	2829 ± 1267	[53]
Moxidectin	Oral	8 mg	SD	26	HV	0.079 ± 0.026	4.89 ± 1.48		700 ± 307	1.78 ± 0.54	1708 ± 724	[53]
Nifurtimox	Oral	15 mg/kg BW	SD	7	HV	0.75 ± 0.25	5.43 ± 2.19		2.95 ± 1.19	193 ± 93	755 ± 283	[54]
Nifurtimox	Oral	30 mg/kg/d	SD	6	Children with refractory or relapsed neuroblastoma	3.28 ± 0.88		15.2 ± 6.5[ei]				[55]
Nifurtimox	Oral	30 mg/kg/d	q8h, MD on d4	6	Children with refractory or relapsed neuroblastoma	4.8 ± 3.48		21.9 ± 13.1[ei]				[55]
Nitazoxanide		500 mg	SD	24	HV	3.31 ± 0.55	15 ± 2.75	13.1 ± 2.66	1.37 ± 0.28			[56]
Nitazoxanide		500 mg	bid, MD on d7	6	HV	9.05 (7.13–11.5)		48.7 (36–66)[tw]	1.8 (1.3–2.6)			[57]
Oxamniquine	Oral	1000 mg	SD	5	HV	1.93 ± 0.28	25,074 ± 4917		1.85 ± 0.24			[58]
Oxamniquine	Oral	1000 mg	SD	9	Advanced hepatosplenic schistosomiasis and periportal hepatic fibrosis	1.27 ± 0.25	20,346 ± 4969		2.52 ± 0.38			[58]
Paromomycin	i.m.	15 mg/kg/d sulfate	SD	6	Visceral leishmaniasis	5.6 ± 4.2						[59]
Paromomycin	i.m.	15 mg/kg/d sulfate	SD	8	HV	23.4 ± 3.9	105 ± 26.3		2.64 ± 0.82	7.56 ± 1.94[d]	30.8 ± 4.5	[60]
Pentamidine	i.v.	2–4.8 mg/kg BW	SD	11	Late-stage African trypanosomiasis	0.92*	5868**		265	67.6	11,850***	[61]
pentamidine	iv	4 mg/kg BW	SD	6	AIDS, Pneumocystis carinii pneumonia				6.4 ± 1.32	248 ± 91	140 ± 93	[62]
Pentamidine	i.m.	4 mg/kg BW	SD	6	AIDS, Pneumocystis carinii pneumonia				9.36 ± 2.01	305 ± 81	924 ± 404	[62]

Table 1 (continued)

Name	Dose			*N*	Health status	C_{max} (μg/mL)	$AUC_{(0-\infty)}$ (μg h/mL)	$AUC_{(0-24)}$ (μg h/mL)	$t_{1/2}$ (h)	Cl (L/h)	*V* (L)	References
Pentamidine	i.m.	3.5–4.5 mg/kg BW	SD	11	AIDS, *Pneumocystis carinii* pneumonia	1242*		6.19**, m				[63]
Pentamidine	i.m.	3.5–4.5 mg/kg BW	q2d, MD after 10 injections	11	African trypanosomiasis	1939*		16.6**, m				[63]
Praziquantel	Oral	40 mg/kg BW	SD	23	HV	0.78 (0.2–1.41)	3.62 (0.61–7.48)	3.61 (0.6–7.48)[t]	1.7 (0.8–3.1)		2093 (1313–10,290)[c]	[41]
Praziquantel	Oral	40 mg/kg BW	SD	9	Hepatosplenic schistosomiasis	1.62 ± 0.39	15.9 ± 5.49		11.9 ± 5.4		3605 ± 1309	[64]
Praziquantel	Oral	25 mg/kg BW	SD	6	HV	0.34 ± 0.084			1.3 ± 0.36			[65]
Praziquantel	Oral	25 mg/kg BW	q8h, MD after 3 doses	10	HV	0.76 ± 0.38		2.84 ± 1.06	3.1 ± 0.8			[66]
Praziquantel	Oral	60 mg/kg/d	q8h, MD after 3 doses	13	Schistosomiasis *Japonicum* infection	2.17 ± 1.14		8.94 ± 4.25	1.7 ± 0.8			[67]
Pyrimethamine	Oral	75 mg	SD	27	HIV + and HIV-, pregnant women		34.7 (26.3–40.6)		95 (80–119)	2.162 (1.85–2.85)	309 (245–372)	[68]
Pyrimethamine	Oral	75 mg	SD	13	HV	0.6 (0.49–0.72)	68.3 (56.6–115)		118 (97–136)	1.09 (0.75–134)	170 (114–227)	[69]
Pyrimethamine	Oral	50 mg	SD	10	HV	0.76 ± 0.15		76 ± 22[un]	114 ± 41.5	0.73 ± 0.22		[70]
Pyrimethamine	Oral	25 mg	SD	12	HV	0.21 ± 0.065	19.1 ± 5.6		95.5 ± 30.6	1.44 ± 0.5	75.9 ± 28.6	[71]
Pyrimethamine	Oral	25 mg	ow, MD after dose 21	6	HV	0.31 ± 0.09		27.8 ± 7.7[t]	123 ± 26.6	1.05 ± 2.25[c]	185 ± 45[c]	[72]
Pyrimethamine	Oral	50 mg/kg/d	od, MD on d21	11	HIV + seropositive for toxoplasma gondii	2.06 ± 0.58	503 ± 325	0.042 ± 0.012	191 ± 115	1.31 ± 0.43	336 ± 180	[73]
Sodium stibogluconate	i.m.	600 mg	SD	29	Cutaneous leishmaniasis	8.77 ± 0.39	37.01 ± 1.57		1.85 ± 0.072	17.7 ± 1.38	45.7 ± 2.62	[74]
Sodium stibogluconate	i.m.	300 mg LD, then 600 mg	od, MD after 3 wk	12	Cutaneous leishmaniasis	7.23 ± 1.58	65.4 ± 8.3	54.2 ± 7.9[t]	8.72 ± 1.44	12.9 ± 1.58	258 ± 44.4	[75]
Sulfadiazine	i.v.	1000 mg	SD	6	HV		510 ± 117		7.03 ± 1.64	2.48 ± 3[c]	21.8 ± 1.2[c]	[76]
Sulfadiazine	Oral	1000 mg	q6h, MD on d5	8	HIV	76.2 ± 26.3		1134 ± 477				[77]

Table 1 (continued)

Name	Dose			*N*	Health status	C_{max} (µg/mL)	$AUC_{(0-\infty)}$ (µg h/mL)	$AUC_{(0-24)}$ (µg h/mL)	$t_{1/2}$ (h)	Cl (L/h)	*V* (L)	References
Suramin	i.v.	d1: 200 mg, then 1 g	Doses on days: 1, 3, 7, 14, 21, 28, 35, MD	4	AIDS				48.5	0.025	38.3	[78]
Tinidazole	i.v.	500 mg	SD	6	HV	7.5 ± 1.2	176 ± 12.7		14 ± 0.7	47.6 ± 2.6	57 ± 1.7	[79]
Tinidazole	Oral	2000 mg	SD	6	HV	40.1 ± 7	733 ± 138		12.3	2.7 ± 5.25[c]	48.8 ± 6[c]	[80]
Tinidazole	Oral	500 mg	SD	9	HV	10.1 ± 0.6	217 ± 15		14.7 ± 0.7			[79]
Triclabendazole sulfoxide	Oral	10 mg/kg BW	SD	12	HV	8.72 ± 1.05		92 ± 18.5 [m]	7.1 ± 0.99			[81]
Triclabendazole sulfoxide	Oral	10 mg/kg BW	SD	20	Fascioliasis	38.6 ± 13.8*		386 ± 159**, [m]	11.2 ± 4.1			[82]

AIDS acquired immune deficiency syndrome, *AUC* area under the concentration–time curve, $AUC_{(0-\infty)}$ AUC from zero to infinity, $AUC_{(0-24)}$ AUC from 0 to 24 h, *bid* twice daily, *BW* bodyweight, *c* calculated from value given per kg by assuming a nominal weight of 75 kg, *Cl* plasma clearance, C_{max} maximum concentration, *CV* coefficient of variation, *d* L/h/1.73 m^2, *d* days, *ei* AUC from 0 to 8 h, *h* hours, *HIV* human immunodeficiency virus, *HV* healthy volunteers, *i.m.* intramuscular, *i.v.* intravenous, *LD* loading dose, *m* AUC from 0 to 48 h, *od* once daily, *ow* once weekly, *q2d* every 2 days, *q6h* every 6 h, *q8h* every 8 h, *Ref* reference, $t_{1/2}$ half-life, *t* AUC from zero to end of dosing interval, *tw* AUC from 0 to 12 h, *un* AUC with undefined time span, *V* volume of distribution, *wk* weeks

*µmol/L; **µmol h/L

Table 2 Tissue penetration of different antiparasitic drugs after single-dose (SD) and/or multiple-dose (MD) administration

Name	Compartment	Dose			*N*	Health status	Transfer rate		$AUC_{compart}/AUC_{plasma}$ Ratio	References
							$C_{compart}/C_{plasma}$ (%)	$C_{compart}/C_{plasma\text{-}ub}$ (%)		
Albendazole sulfoxide	CSF	Oral	15 mg/kg/d	q8h, MD on d7	18	Parenchymal brain neurocysticercosis	43*			[83]
Albendazole sulfoxide	CSF	Oral	200 mg	bid, MD	1	Child with cerebral echinococcosis	50*			[84]
Albendazole sulfoxide	Cyst fluid	Oral	200 mg	bid, MD	1	Child with cerebral echinococcosis	40*			[84]
Albendazole sulfoxide	Cyst fluid	Oral	10 mg/kg/d	bid, MD after 36 h	7	Hydatid cyst	13*			[85]
Albendazole sulfoxide	Cyst fluid	Oral	10 mg/kg/d	bid, MD	12	Hydatid cyst	22*			[85]
Albendazole sulfoxide	Cyst fluid	Oral	10 mg/kg/d	MD	3	Hydatid cyst	19.5*			[86]
Albendazole sulfoxide	Breast milk	Oral	400 mg	SD	23	Healthy lactating women	60 (10–150)			[87]
Amphotericin B deoxycholate	Bile	i.v.	250 mg	SD	1	Critically ill			0.15	[88]
Liposomal amphotericin B	Bile	i.v.	400 mg (LD 200 mg)	od, MD on d4	1	Critically ill			0.05	[88]
Liposomal amphotericin B	ELF	i.v.	309 ± 22 mg	od, MD	11	Critically ill	61 ± 25	154 ± 44[lib]		[89]
Liposomal amphotericin B	Uninfected lung tissue	i.v.	250 mg	SD	1	Esophageal cancer, aspergillosis	140			[90]
Liposomal amphotericin B	Infected lung tissue	i.v.	250 mg	SD	1	Esophageal cancer, aspergillosis	520			[90]
Liposomal amphotericin B	Buccal mucosal tissue	i.v.	15 mg/kg BW	SD	6	Peripheral stem cell transplant	16.3 ± 7.9			[32]
Liposomal amphotericin B	Buccal mucosal tissue	i.v.	7.5 mg/kg BW	ow, MD on d7	4	Peripheral stem cell transplant	47.2 ± 48.5			[32]
Liposomal amphotericin B	Buccal mucosal tissue	i.v.	1 mg/kg BW	od, MD on d7	6	Peripheral stem cell transplant	6.2 ± 8.6			[32]
Liposomal amphotericin B	Buccal mucosal tissue	i.v.	7.5 mg/kg BW	ow, MD on d15	4	Peripheral stem cell transplant	22.8 ± 18.6			[32]
Liposomal amphotericin B	Buccal mucosal tissue	i.v.	1 mg/kg BW	od, MD on d15	6	Peripheral stem cell transplant	10.6 ± 6.3			[32]
Liposomal amphotericin B	CSF	i.v.	3 mg/kg/d	q2d, MD	14	Pediatric haemato-oncological	13 (2–92)			[91]

Table 2 (continued)

Name	Compartment	Dose			*N*	Health status	Transfer rate		$AUC_{compart}/AUC_{plasma}$ Ratio	References
							$C_{compart}/C_{plasma}$ (%)	$C_{compart}/C_{plasma\text{-}ub}$ (%)		
Liposomal amphotericin B	Burn eschar	i.v.	2.04 mg/kg BW	od, MD	1	Severely burned	899			[92]
Amphotericin B lipid complex	ELF	i.v.	300 ± 47 mg	od, MD	5	Critically ill	447 ± 224			[89]
Amphotericin B colloidal dispersion	ELF	i.v.	279 ± 16 mg	od, MD	28	Critically ill	125 ± 52	153 ± 53[lib]		[89]
Amphotericin B colloidal dispersion	Bile	i.v.	250 mg	od, MD on d7	1	Critically ill			0.28	[88]
Amphotericin B colloidal dispersion	Bile	i.v.	200 mg	od, MD on d5	1	Critically ill			0.12	[88]
Benznidazole	Breast milk	Oral	5–8 mg/kg BW	bid, MD	12	Lactating women with Chagas disease	52 (IQR 47–129)			[93]
Diethylcarbamazine	Saliva	Oral	150 mg	SD	6	HV			*0.26*[c]	[94]
Eflornithine	CSF	i.v.	200 mg	bid, MD on d13–14	40	Adults with T.b. gambiense sleeping sickness	90 ± 47			[95]
Eflornithine	CSF	i.v.	200 mg	bid, MD on d 13–14	10	Children with T.b. gambiense sleeping sickness	58 ± 38			[95]
Ivermectin	Stratum corneum	Oral	207.3 ± 20.4 mg/kg BW	SD	13	Scabies	162*,[c]			[96]
Ivermectin	Breast milk	Oral	150 mg/kg BW	SD	4	HV	51 ± 6			[97]
Mebendazole	Cyst	Oral	48 mg/kg/d	q8h, MD	22	Echinococcal infection	59.8*,[c]			[98]
Melarsoprol	CSF	i.v.	Treatment schedule according to national treatment guidelines of East Africa	MD	16	Second-stage *Typanosoma brucei gambiense* infection	4.2*,[c]			[47]
Metronidazole	Brain ECF	i.v.	500 mg	tid, MD on d3–6	4	Acute brain injury			1.02 ± 0.19[Aτ, ubb]	[99]
Metronidazole	CSF	i.v.	500 mg	tid, MD on d2–5	4	Acute brain injury			0.86 ± 0.16[Aτ, ubb]	[100]
Metronidazole	CSF	Oral	2400 mg	SD	4	Diagnostic lumbar puncture	43*			[101]

Table 2 (continued)

Name	Compartment	Dose			*N*	Health status	Transfer rate		$AUC_{compart}/AUC_{plasma}$ Ratio	References
							$C_{compart}/C_{plasma}$ (%)	$C_{compart}/C_{plasma\text{-}ub}$ (%)		
Metronidazole	Muscle	i.v.	500 mg	SD	6	Septic shock			$0.88 \pm 0.47^{At, ub}$	[102]
Metronidazole	Muscle	i.v.	500 mg	SD	6	Female patients scheduled for elective gynecologic surgery			$0.73 \pm 0.16^{At, ub}$	[103]
Metronidazole	Subcutis	Oral	2 g	SD	10	HV			$0.67 \pm 0.2^{Aei, ub}$	[104]
Metronidazole	Milk	Oral	400 mg	tid, MD on d4	12	Breast-feeding	88 ± 4			[105]
Moxidectin	Breast milk	Oral	8 mg	SD	12	HV			1.77 ± 0.66	[106]
Pentamidine base	CSF	i.m.	3.5–4.5 mg/kg BW	q2d, MD after 10 injections	5	*Trypanosoma brucei gambiense* infection without involvement of the central nervous system	0.5–0.8			[63]
Praziquantel	CSF	Oral	25 mg/kg BW	q6h, MD on d10	8	Neurocysticercosis	12.3 ± 3.8			[107]
Praziquantel	CSF	Oral	50 mg/kg/d	q8h, MD on d6	11	Parenchymal brain neurocysticercosis	24*			[83]
Praziquantel	CSF	Oral	50 mg/kg/d	tid, MD on d21	10	Neurocysticercosis	13.1 ± 2.2			[108]
Praziquantel	Breast milk	Oral	50 mg/kg BW	SD	5	Healthy lactating women			0.313	[109]
Praziquantel	Breast milk	Oral	20 mg/kg BW	SD	5	Healthy lactating women			0.244	[109]
Pyrimethamine	Brain tissue	Oral	100 mg	SD	16	Patients with HIV undergoing neurosurgery	5.2*			[110]
Pyrimethamine	CSF	Oral	50 mg/kg/d	MD after ≥ 2 wk	2	Acute toxoplasma encephalitis in patients with AIDS	24*			[111]
Pyrimethamine	CSF	Oral	25 mg/kg/d	MD after ≥ 2 wk	3	Acute toxoplasma encephalitis in patients with AIDS	14.1*			[111]
Pyrimethamine	Saliva	Oral	25 mg	SD	6	HV	26.2 ± 1.6			[112]
Pyrimethamine	Breast milk	Oral	12.5 mg	SD	3	Lactating women			0.46–0.66	[113]
Sodium stibogluconate	Normal skin	i.m.	600 mg	od^{nd}	9	Cutaneous leishmaniasis			1.13 (SEM 0.39)^{Ai}	[114]

Table 2 (continued)

Name	Compartment	Dose			*N*	Health status	Transfer rate		$AUC_{compart}/AUC_{plasma}$ Ratio	References
							$C_{compart}/C_{plasma}$ (%)	$C_{compart}/C_{plasma\text{-}ub}$ (%)		
Sodium stibogluconate	Skin lesion	i.m.	600 mg	od[nd]	9	Cutaneous leishmaniasis			0.86 (SEM 0.16)[Ai]	[114]
Sulfadiazine	Leg lymph	Oral	820 mg	SD	5	HV			0.63 ± 0.17[Atw]	[115]
Sulfadiazine	Leg lymph	Oral	820 mg	od, MD on d4	5	HV			0.68 ± 0.12[Atw]	[115]
Tinidazole	Breast milk	i.v.	1600 mg	SD	5	Women undergoing acute Caesarean section	62–139			[116]
Tinidazole	CSF	Oral	2000 mg	SD	4	Diagnostic lumbar puncture	88*			[101]
Tinidazole	Skin blister fluid	Oral	2000 mg	SD	11	HV			1 ± 0.1	[117]

Aei AUC ratio for AUC from 0 to 8 h, *Ai* AUC ratio for AUC from zero to infinity, *At* AUC ratio for AUC from 0 to 10 h, *Atw* AUC ratio for AUC from 0 to 12 h, A^{τ} AUC ratio for AUC from dosing time to dosing interval, *AUC* area under the concentration–time curve, *bid* twice daily, *BW* bodyweight, *c* calculated from values given in the original publication, $C_{compart}$ drug concentration in respective compartment, C_{plasma} drug concentration in plasma, $C_{plasma\text{-}ub}$ unbound drug concentration in plasma, *CSF* cerebrospinal fluid, *d* days, *ECF* extracellular fluid, *ELF* epithelial lining fluid, *h* hours, *HV* healthy volunteers, *IQR* interquartile range, *i.m.* intramuscular, *i.v.* intravenous, *LD* loading dose, *lib* liberated fraction, *nd* not defined if SD or MD pharmacokinetic data, *od* once daily, *ow* once weekly, *q2d* every 2 h, *q6h* every 6 h, *q8h* every 8 h, *Ref* reference, *SEM* standard error of the mean, *tid* three times daily, *ub* AUC in compartment calculated from unbound drug concentrations, *ubb* AUC in compartment and plasma calculated from unbound drug concentrations, *wk* weeks

*Value given as mean

Table 3 Pharmacokinetic parameters of different antiparasitic drugs in patients with organ impairment

Name	Dose			*N*	Health status	Cl_{Cre} (mL/min)	C_{max} (μg/mL)	$AUC_{(0–24)}$ (μg h/mL)	$t_{1/2}$ (h)	Cl (L/h)	*V* (L)	References
Diethylcarbamazine	Oral	50 mg	SD	5	Moderate renal impairment	25–60		2.8 ± 1.5^{Ai}	7.7 ± 4.1			[118]
Diethylcarbamazine	Oral	50 mg	SD	7	Severe renal impairment	< 25		3.4 ± 2.2^{Ai}	15.14 ± 7.7			[118]
Metronidazole	i.v.	500 mg	SD	8	Liver cirrhosis and coma				20 ± 9	1.74 ± 0.6	44 ± 9	[119]
Metronidazole	i.v.	500 mg	SD	29	Moderate renal impairment	26 ± 10		159 ± 52^{un}	7.4 ± 2.4	3.6 ± 1.2	36 ± 9.4	[120]
Metronidazole	i.v.	500 mg	SD	29	Severe renal impairment	5.3 ± 2.5		180 ± 82^{un}	11 ± 5.7	4.1 ± 3.5	48 ± 20	[120]
Metronidazole	i.v.	500 mg	SD	29	renal failure	< 1		99 ± 27^{un}	7.2 ± 2.3	5.5 ± 1.7	55 ± 21	[120]
Metronidazole	i.v.	500 mg	SD	14	Child-Pugh A			124.9 ± 42.3	10.7 ± 2.3	3.83 ± 1.17^{c}	55.5 ± 8.3^{c}	[121]
Metronidazole	i.v.	500 mg	SD	9	Child-Pugh B			124.4 ± 25.8	13.5 ± 5.1	3.56 ± 1.62^{c}	59.3 ± 9^{c}	[121]
Metronidazole	i.v.	500 mg	SD	12	Child-Pugh C			174.1 ± 52	21.5 ± 12.7	2.52 ± 1.26^{c}	60.8 ± 10.5^{c}	[121]
Metronidazole	i.v.	500 mg	SD	10	Schistosomiasis			135 ± 33.8	10.2 ± 2.1	4.19 ± 0.86^{c}	59.3 ± 6.8^{c}	[121]
Metronidazole	i.v.	8 mg/kg BW	SD	10	Alcoholic liver disease or chronic active hepatitis	32–84			19.9 ± 2.5	1.05 ± 0.14^{c}	28.5 ± 2.3^{c}	[122]
Metronidazole	i.v.	7.5 mg/kg BW	SD	8	Alcoholic liver disease	82.3 ± 16.8		256.8 ± 56.3^{Ai}	18.31 ± 6.06	2.3 ± 0.5^{c}	57.8 ± 12^{c}	[123]
Metronidazole	Oral	500 mg	SD	6	Hepatosplenic schistosomiasis			128.7 ± 18^{Ai}	8.4 ± 1.3	5.5 ± 0.7^{c}	59.3 ± 3.8^{c}	[51]
Metronidazole	Oral	500 mg	SD	6	Liver cirrhosis			157.8 ± 36.6^{Ai}	10.8 ± 2.4	5.2 ± 1.2^{c}	55.5 ± 3^{c}	[51]
Pentamidine	i.v.	4 mg/kg BW	SD	2	Impaired renal function, AIDS, *Pneumocystis carinii* pneumonia	73.5*			7.5*	198.5*	234*	[124]
Pentamidine	i.m.	4 mg/kg BW	SD	2	Impaired renal function, AIDS, *P. carinii* pneumonia	62.3*			11.1*	300*	1259*	[124]
Praziquantel	Oral	60 mg/kg/d	MD	13	Inapparent liver disease and *Schistosoma japonicum* infection		2.17 ± 1.14	8.94 ± 4.25	1.7 ± 0.8			[67]
Praziquantel	Oral	60 mg/kg/d	MD	9	Moderate liver disease and *S. japonicum* infection		5.01 ± 2.47	22.88 ± 15.82	2.2 ± 0.6			[67]
Praziquantel	Oral	60 mg/kg/d	MD	8	Severe liver disease and *S. japonicum* infection		8.195 ± 4.86	37.77 ± 24.5	2.3 ± 1.0			[67]
Tinidazole	i.v.	800 mg	SD	12	Chronic renal failure	19.44*	22.6 ± 1.64	379.6 ± 19.9^{un}	15.09 ± 0.68	2.26 ± 0.14^{c}	27 ± 3.2	[14]
Tinidazole	i.v.	800 mg	SD	9	Severe chronic renal failure	12.44*	25.5 ± 9.8	435 ± 51^{un}	16.86 ± 4.91	1.86 ± 0.21	51.75 ± 6.75^{c}	[15]

Ai AUC from zero to infinity, *AIDS* acquired immune deficiency syndrome, *AUC* area under the concentration–time curve, $AUC_{(0–24)}$ AUC from 0 to 24 h, *BW* bodyweight, *c* calculated from value given per kg by assuming a nominal weight of 75 kg, *Cl* plasma clearance, Cl_{Cre} creatinine clearance, C_{max} maximum concentration, *d* days, *h* hours, *i.m.* intramuscular, *i.v.* intravenous, *MD* multiple dose, *Ref* reference, *SD* single dose, $t_{1/2}$ half-life, *un* AUC with undefined time span, *V* volume of distribution

*Value given as mean

Diethylcarbamazine can be used for the treatment of different filarial diseases, such as lymphatic filariasis, loiasis, tropical pulmonary eosinophilia, and onchocerciasis. No tissue PK studies could be identified that met our requirements, except for one study that investigated the penetration of DEC into saliva (Table 2). Tissue penetration of the drug would however be crucial to successfully treat the above-named parasitic infections.

3.5 Eflornithine

Eflornithine (EFO) can be administered orally or intravenously. It is used for the treatment of African trypanosomiasis (HAT) caused by *Trypanosoma brucei gambiense*. Only one plasma PK study after multiple administration of the drug has been identified that provides sufficient detail (Table 1).

Trypanosomes can cross the blood–brain barrier and penetrate into the CSF leading to neurological symptoms. To treat those infections, sufficiently high drug concentrations in CSF are of utmost importance. Two studies were identified that investigated CSF concentrations of EFO (Table 2).

3.6 Fexinidazole

Fexinidazole (FEX) is a 5-nitroimidazole derivative and can only be administered orally. It was approved in 2018 for the treatment of *Trypanosoma brucei gambiense* HAT and is the most recent key achievement of the Drugs for Neglected Diseases Initiative. It is of high value for HAT endemic countries because it is the first entirely oral treatment for *T. brucei gambiense* HAT and showed promising results in a number of clinical trials. Pharmacokinetic data for SD and MD administration are provided in Table 1.

For the treatment of stage II HAT, penetration through the blood–brain barrier is necessary. However, to date, no human PK studies have investigated FEX PK in CSF or brain tissue.

3.7 Ivermectin

Ivermectin (IVM) is available as an oral and topical formulation. Depending on the indication, doses ranging from 150 to 400 µg/kg bodyweight are used, either as a SD or in dosing intervals of 2 weeks up to 2 years. If used for the treatment of *Strongyloides stercoralis* hyperinfection syndrome and/or disseminated disease, 200 µg/kg bodyweight per day for at least 2 weeks is the recommended dose. Ivermectin should be administered in fasting conditions to increase bioavailability. Studies reporting human SD pharmacokinetics of IVM for different doses are presented in Table 1.

Ivermectin is effective against a number of parasites, including *Onchocerca volvulus, Wuchereria bancrofti*, and *Brugia malayi*, and different intestinal helminths and ectoparasites. Although tissue PK data for different compartments would be of interest, only one study on breast milk penetration and one study on skin penetration could be identified that provide sufficient data to be included in this review (Table 2).

3.8 Mebendazole

Mebendazole (MEB) belongs to the group of benzimidazoles and is currently available as an oral formulation. The corresponding PK data after oral administration are provided in Table 1. Depending on the indication, it is used in different dosages.

This antiparasitic drug in mainly used for the treatment of infections with nematodes and cestodes, namely echinococcosis, toxocariasis, and trichinellosis. Therefore, penetration of MEB into CSF, cyst fluid in the liver and lung, muscle tissue, eye, and different other organs is crucial for the antiparasitic effects of MEB. Pharmacokinetic studies on tissue penetration of MEB are very limited and only available for echinococcal cyst fluid (Table 2).

3.9 Melarsoprol

Melarsoprol (MSP) is an arsenical compound that is available for intravenous injection and is highly toxic. Several different treatment regimens are being used. The PK data after a typical treatment regimen are presented in Table 1. Melarsoprol is used for the management of stage II HAT and one study investigating penetration of MSP into human CSF could be identified (Table 2).

3.10 Metronidazole

Metronidazole (MDZ) belongs to the nitroimidazoles and is the most frequently used member of this group. Metronidazole exhibits antibacterial and antiprotozoal activity. It is available for intravenous (i.v.) infusion and oral administration. Doses ranging from 250 mg to 2 g are routinely used clinically depending on the indication. Pharmacokinetic data after i.v. and oral administration are presented in Table 1. Multiple plasma PK studies in patients with decreased liver and renal function are available and presented in Table 3. One study was excluded from the table because PK data from patients with liver impairment and renal insufficiency were mixed [9].

Regarding the antiparasitic use of MDZ, the main indications are invasive amoebiasis and giardiasis. The protozoan parasite *Giardia lamblia* that causes giardiasis does not invade extraintestinal tissue. However, for the treatment of amoebiasis, penetration of MZD into liver abscesses and in

some cases brain tissue is essential. The PK data for MDZ in brain tissue, CSF, and muscle tissue are presented in Table 2.

3.11 Miltefosine

Miltefosine (MTF) is only available as an oral formulation. The recommended dose is 50 mg either twice a day or three times a day for 28 days, depending on the weight of the patient. Human PK data for MD administration of MTF are provided in Table 1.

The primary indication for the use of MTF is cutaneous and visceral leishmaniasis. Pharmacokinetic studies that investigated the penetration of MTF into tissue could not be identified in the current literature.

3.12 Moxidectin

Moxidectin (MOX) is an anti-helminthic drug that is only available as an oral formulation. The recommended dose is 8 mg as a single dose. The corresponding PK data are provided in Table 1.

Moxidectin was recently approved for the treatment of onchocerciasis in the USA. Target sites for the treatment of onchocerciasis are the skin, lymph nodes, and the eye. Currently, there are no PK studies in these compartments published; however, penetration data of MOX into human breast milk are presented in Table 2.

3.13 Nifurtimox

Nifurtimox (NFT) is available in an oral form and usually administered in doses ranging from 8 to 20 mg/kg bodyweight per day in three or four divided doses depending on the age of the patients. Single-dose and MD PK data are given in Table 1.

Nifurtimox is primarily used for the treatment of American trypanosomiasis, also named Chagas disease. Unfortunately, we could not identify any relevant tissue penetration studies for NFT.

3.14 Nitazoxanide

Nitazoxanide (NZX) is an anti-parasitic and anti-viral drug that is used as an oral dose of 500 mg twice daily. Single-dose and MD human PK studies are given in Table 1. The drug is indicated for the treatment of amoebiasis and giardiasis, but no thorough tissue PK studies could be identified.

3.15 Oxamniquine

Oxamniquine (OXA) is an anti-schistosomal drug that is used as an oral dose of 15–60 mg/kg bodyweight. Single-dose PK data in healthy volunteers (HV) and patients with advanced hepatosplenic schistosomiasis are presented in Table 1.

Relevant tissue PK studies for OXA could not be identified. This might be attributable to the fact that OXA is primarily indicated for use in intestinal schistosomiasis.

3.16 Paromomycin

Paromomycin (PAM) is available as an oral capsule and a formulation for intramuscular (i.m.) injection. The recommended i.m. dose is 15 mg/kg bodyweight of PAM sulfate once per day. The usual oral dose is 25–35 mg/kg bodyweight per day of PAM sulfate in three divided doses. It has to be noted that 11 mg of PAM base are equivalent to 15 mg of PAM sulfate. In Table 1, human PK data after i.m. SD administration of PAM to HV and patients with visceral leishmaniasis are presented. Absorption of PAM after oral administration has been reported to be negligible [10].

The indications for treatment with PAM are visceral leishmaniasis, giardiasis, intestinal amebiasis, and cryptosporidiosis. Yet, tissue PK studies for PAM are currently missing.

3.17 Pentamidine

Pentamidine (PMD) is an antiprotozoal and anti-pneumocystis drug that is available as a formulation for an i.v. or i.m. injection and inhalation. The usual clinical dose is 4 mg/kg bodyweight of PMD per day as an i.v. or i.m. injection. Pharmacokinetic studies after SD and MD administration of PMD to *T. brucei gambiense*- and *Pneumocystis carinii*-infected patients could be identified (Table 2).

For the treatment of African trypanosomiasis, penetration of the blood–brain barrier would be beneficial. In the current literature, one study could be identified that investigated penetration of PMD into CSF (Table 2).

One study was excluded from the data of patients with organ impairment shown in Table 3. This study reported a volume of distribution at steady state of 32.4 ± 45.3 L, a clearance of 329 ± 58 L/h, and an AUC from zero to infinity of 0.75 ± 0.16 µg h/mL for patients undergoing long-term hemodialysis [11].

3.18 Pentavalent Antimony

Pentavalent antimony (SbV) can be administered as meglumine antimoniate (MA) or sodium stibogluconate and formulations for i.v., i.m., and intralesional applications are available. The usual dose of SbV is 20 mg/kg bodyweight per day for 10–28 days. Pharmacokinetic data for the i.m. injection of MA and sodium stibogluconate are provided in Table 1.

Pentavalent antimony is used for the treatment of visceral, cutaneous, and mucocutaneous leishmaniasis. Hence, penetration of SbV into soft tissue, liver, spleen, bone marrow, and lymph nodes would be beneficial. Only two skin penetration studies on sodium stibogluconate (Table 2) and one skin penetration study on MA could be identified. However, the study on MA was not included because of the poor quality of the data. No other tissue penetration studies were found.

3.19 Praziquantel

Praziquantel (PZQ) exhibits antiparasitic activity and is used in a variety of different dosing regimens. Doses typically range from 15 to 40 mg/kg bodyweight several times per day. For population-based treatment of *Opisthorchis viverrini*, a SD of 40 mg/kg is recommended. The SD and MD PK data after different doses of PZQ are presented in Table 1.

Praziquantel is used to treat schistosomiasis, intestinal fluke infections, liver fluke infections, paragonimiasis, and cysticercosis. Target sites for the treatment of these infections include virtually every organ, but the most important are the biliary system, the liver, the lung, and the central nervous system. In the currently available literature, tissue PK studies in CSF and human breast milk were identified (Table 2). Two studies investigating the concentration of PZQ in cyst fluid in patients with cysticercosis were excluded from Table 2 because of the poor quality of the data [12, 13].

3.20 Pyrimethamine

Pyrimethamine (PYM) is administered orally and given in doses ranging from 25 to 75 mg. A loading dose of 200 mg of PYM is recommended in some cases. It is usually given in combination with sulfadiazine. The data from different plasma PK studies after SD and MD of PYM for different doses are provided in Table 1.

The main antiparasitic indication for PYM use is toxoplasmosis. Toxoplasmosis cysts mainly appear in the brain, eye, bone, and cardiac muscle. Tissue PK studies in CSF, brain tissue, saliva, and human breast milk are available in the literature; however, PK data for the other compartments could not be identified (Table 2).

3.21 Sulfadiazine

Sulfadiazine (SDZ) is available as an oral and i.v. formulation and is administered in doses from 1 to 1.5 g four times per day. Plasma PK parameters after SD and MD administration in HV are available in the literature (Table 1).

For the treatment of parasitic diseases, it is primarily used for toxoplasmosis in combination with PYM. Tissue penetration studies in leg lymph nodes after SD and MD administration are given in Table 2.

3.22 Suramin

Suramin (SUR) is administered as an i.v. infusion of 20 mg/kg bodyweight after administration of a test dose of 5 mg/kg bodyweight. Only one plasma PK study after MD administration of SUR was identified (Table 1). Suramin is indicated for the treatment of stage I HAT; however, no tissue penetration studies for SUR were found.

3.23 Tinidazole

Tinidazole (TDZ) belongs to the group of nitroimidazoles and can be administered as an oral or i.v. formulation. The usual dose is 2 g of TDZ four times per day. Plasma PK data after oral and i.v. SD are given in Table 1.

Tinidazole is approved for the treatment of giardiasis, amebiasis, and trichomoniasis. Different tissue penetration studies for TDZ are available (Table 2).

Two PK studies were excluded from Table 3 because they were performed in a patient undergoing hemodialysis. In the first study, a single dose of 800 mg of tinidazole was intravenously administered to patients undergoing hemodialysis. In this study, a half-life of 4.25 ± 0.43 h and 12.9 ± 1 h was reported during and after dialysis, respectively. Additionally, a dialysis clearance of 49.9 ± 3.2 mL/min was reported [14]. The second study in patients undergoing hemodialysis was conducted after oral administration of 2 g of tinidazole. This dosage led to a half-life between dialysis of 18.37 ± 3.54 h and a dialysis clearance of 71 ± 7.7 mL/min [15].

3.24 Triclabendazole

Triclabendazole (TBD) is a member of the benzimidazoles and is usually administered as an oral dose of 10 mg/kg bodyweight. The corresponding plasma pharmacokinetics after SD administration are shown in Table 1.

Triclabendazole is typically used for the treatment of fascioliasis and paragonimiasis. Therefore, good penetration of TBD into the biliary system, the liver, the lung, and the brain would be beneficial. However, no tissue PK studies for TBD could be identified.

4 Discussion

Parasites can invade virtually every organ and cause infections that impair the quality of life and even cause death. Many different anti-parasitic agents are available to treat those infections. However, most of these agents were developed decades ago. Some even go back to the very beginnings

of anti-infective chemotherapy. Despite their long availability, for many drugs, penetration into the particular target tissue has not been investigated. Yet, to effectively treat a parasitic infection, the anti-parasitic agent has to reach the tissue where the parasite resides in sufficiently high concentrations. Knowledge of the amount of tissue penetration would therefore allow for informed analysis of the available treatment schemes and could help optimize treatment of parasitic diseases.

Particularly, knowledge of penetration into CSF and brain tissue would be of immense value for ALB, BZD, EFO, FEX, IVM, MEB, MSP, MDZ, NFT, NZX, PMD, PZQ, PYM, SDZ, SUR, and TDZ. All of these drugs are used for the treatment of diseases that affect the central nervous system. The penetration into the liver or the biliary system is especially interesting for ALB, MEB, MDZ, MTF, NZX, PAM, SbV, PZQ, TDZ, and TBD because those drugs target parasites that regularly invade the liver and biliary system. Lung penetration is pivotal for ALB, AmB, DEC, MEB, PZQ, and TBD, whereas the eye is an important target organ for ALB, DEC, IVM, MEB, MOX, PYM, and SDZ. Penetration of lymphatic tissue and soft tissue is essential for ALB, AmB, DEC, IVM, MTF, MOX, PAM, SbV and ALB, BZD, DEC, IVM, MTF, MOX, PAM, SbV, PZQ, PYM, SDZ, respectively. Evidently, there is an enormous need for tissue PK studies in the field of antiparasitic chemotherapy. The available PK tissue studies on these agents are accumulated in Table 2 and this table clearly shows that for many of the drugs, proper tissue PK studies are lacking. We encourage scientists to fill that gap and help optimize the treatment of parasitic diseases and thereby improve patient care worldwide.

Apart from the PK data of the drug, knowledge of the PK/pharmacodynamic (PD) relationship of the antimicrobial agent is a prerequisite to employ target attainment analysis and evaluate the existing treatment schemes. The focus of the current review lies on the pharmacokinetics of antiparasitic drugs, yet from a non-systematic screening of literature it is obvious that in contrast to anti-bacterial drugs, the PK/PD indices that define the efficacy of antiparasitic drugs, have only been investigated very sparsely. More extensive PK/PD analyses are only available for antimalarial drugs, which are not included in the current review. The PK/PD index for AMB has only been investigated for the treatment of fungal infections, but not against parasites. A number of studies demonstrated concentration-dependent antifungal activity of AMB with the peak concentration divided by the minimal inhibitory concentration correlating best with AMB activity [16–18]. For BZD, NFT, and FEX, there is only a single study investigating the relevant PK/PD index. The authors of this study developed a novel time-to-kill assay and were able to show that BDZ, NFT, and FEX all exhibit concentration-dependent trypanocidal activity [19]. The PK parameter of EFO that correlates best with the probability of being cured from late-stage *T. brucei gambiense* sleeping sickness is the AUC for a dosing interval, according to one study from 2014 [20]. This finding indicates that a combination of concentration and time dependency defines the trypanocidal activity of EFO. The authors developed a population PK model and discovered that a AUC for a dosing interval of the enantiomer L-EFO of > 800 h µmol/L was required for cure [20]. Repurposing of IVM for mass administration to tackle malaria has been proposed, as IVM has been shown to kill *Anopheles* mosquitos feeding on human blood for 28 days after treatment [21]. The PK/PD properties of IVM have been investigated in a recent trial for its mosquitocidal activity and this analysis showed a time-independent relationship of IVM [22]. However, no data on the PK/PD properties of IVM for antiparasitic use are available in the literature. Concentration-dependent activity was demonstrated for MTZ against the parasite *Trichomonas vaginalis* with maximum activity at 10–25 times the minimum lethal concentration [23].

The successful treatment of leishmaniasis requires sufficient drug concentrations inside of phagocytes. For MTF, plasma and intracellular human peripheral blood mononuclear cell concentrations are highly correlated and a plasma AUC from day 0 to 28 of 535 mg d/L has been proposed as a PK target [24, 25]. The PK/PD relationship of PZQ was investigated in a *Schistosoma mansoni* mouse model. The authors of the study demonstrated that plasma exposure is not predictive of PZQ anti-schistosomal activity in the mouse model and concluded that the concentration of PZQ in the mesenteric veins (target compartment for *S. mansoni* infections) is probably the driver of efficacy [26]. In contrast to this, a population PK study found a strong correlation of drug AUC in the plasma and parasitological cure of pediatric patients with intestinal schistosomiasis [27]. For the remaining antiparasitic agents, there is a void of studies investigating the PK/PD relationship that urgently needs to be filled to improve the treatment of patients infected with parasitic diseases worldwide.

5 Conclusions

The current review provides extensive plasma and tissue PK data of antiparasitic drugs and summarizes the currently available literature on the PK/PD relationship of these drugs. There is a considerable amount of data on plasma PK of antiparasitic agents available, but tissue PK has not been thoroughly explored. In addition, there is a lack of studies that investigate the PK/PD relationship of antiparasitic drugs. To improve the treatment of patients with parasitic diseases, we encourage scientists to help fill this gap.

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