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REVIEW ARTICLE

Clinical Pharmacokinetics of Systemically Administered Antileishmanial Drugs

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Abstract This review describes the pharmacokinetic properties of the systemically administered antileishmanial drugs pentavalent antimony, paromomycin, pentamidine, miltefosine and amphotericin B (AMB), including their absorption, distribution, metabolism and excretion and potential drug–drug interactions. This overview provides an understanding of their clinical pharmacokinetics, which could assist in rationalising and optimising treatment regimens, especially in combining multiple antileishmanial drugs in an attempt to increase efficacy and shorten treatment duration. Pentavalent antimony pharmacokinetics are characterised by rapid renal excretion of unchanged drug and a long terminal half-life, potentially due to intracellular conversion to trivalent antimony. Pentamidine is the only antileishmanial drug metabolised by cytochrome P450 enzymes. Paromomycin is excreted by the kidneys unchanged and is eliminated fastest of all antileishmanial drugs. Miltefosine pharmacokinetics are characterized by a long terminal half-life and extensive accumulation during treatment. AMB pharmacokinetics differ per drug formulation, with a fast renal and faecal excretion of AMB deoxylate but a much slower clearance of liposomal AMB resulting in an approximately ten-fold higher exposure. AMB and pentamidine pharmacokinetics have never been evaluated in leishmaniasis patients. Studies linking exposure to effect would be required to define target exposure levels in dose optimisation but have only been performed for miltefosine. Limited research has been conducted on exposure at the drug's site of action, such as skin exposure in cutaneous leishmaniasis patients after systemic administration. Pharmacokinetic data on special patient populations such as HIV co-infected patients are mostly lacking. More research in these areas will help improve clinical outcomes by informed dosing and combination of drugs.

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Key Points

Due to very limited treatment options for leishmaniasis patients, optimisation of current drug dosages and drug combinations is of utmost importance, for which this review provides a solid pharmacokinetic basis.

This review describes the absorption, distribution, metabolism and excretion, as well as the clinical pharmacokinetics and potential drug–drug interactions of the antileishmanial drugs pentavalent antimonials, paromomycin, pentamidine, miltefosine and amphotericin B in the context of leishmaniasis.

The pharmacokinetics of two out of five antileishmanial drugs have never been evaluated in leishmaniasis patients. Exposure–response studies and pharmacokinetic data in special patient populations such as HIV co-infected patients are lacking. More research in this area will improve clinical outcomes via informed dosing regimens and combinations of drugs.

1 Introduction

Leishmaniasis is a neglected tropical disease caused by the *Leishmania* parasite and can cause diverse clinical manifestations depending on the subspecies responsible for the infection and the host immune response. The two main types are the systemic disease visceral leishmaniasis (VL) and the skin infection cutaneous leishmaniasis (CL). Several drugs (Table 1) are currently used in clinical practice in treatment of both VL and CL [1, 2] but clinical guidelines differ by region. Clinical results obtained in one area of endemicity cannot be extrapolated to other geographical areas as efficacies have been shown to vary widely between countries and parasite subspecies (reviewed in Croft and Olliaro [3] and Sundar and Singh [4]).

Rising levels of resistance against antimonials, mostly in India, and potentially miltefosine, is a great pitfall in the treatment of leishmaniasis patients [4, 5]. Available treatment options are limited, especially in vulnerable patient populations such as paediatric leishmaniasis patients and HIV patients co-infected with VL. Therefore, several new combinations of drugs are currently being tested to improve the efficacy of antileishmanial therapies. Furthermore, combination therapies could possibly shorten treatment duration.

Table 1 Overview of antileishmanial drugs systemically administered in treatment of visceral and/or cutaneous leishmaniasis (only includes information in human subjects, unless indicated otherwise)

Antileishmanial drug	Formulations	Route of administration	Distribution		Metabolism	Excretion
			Highest accumulation	Skin		
Pentavalent antimonials	Sodium stibugluconate (SSG) Meglumine Antimoniate (MA)	IM/IV	Liver, thyroid, heart	Confirmed	Intracellular reduction to Sb^{III}	Renal clearance
Paromomycin	Paromomycin sulphate	IM	Not reported	Not reported	Not metabolized	Renal clearance
Pentamidine	Pentamidine dimesylate Pentamidine isethionate	IM/IV	Kidney, liver, spleen, adrenal glands	Not reported	CYP1A1 (CYP2D6, CYP3A5 and CYP4A11)	Not excreted unchanged
Miltefosine	Miltefosine	Oral	Not reported (rats/mice: kidney, liver, spleen, intestines, adrenal)	Not reported (in rats: confirmed)	Intracellularly by phospholipase D	Not excreted unchanged (metabolised to endogenous compounds)
Amphotericin B[a]	D-AMB L-AMB	IV	Liver, spleen	Not reported (in rats: confirmed)	Metabolism not well-studied. Liposomes engulfed by RES	D-AMB: urinary excretion (21%); faecal excretion (43%) L-AMB: urinary excretion (5%); faecal excretion (4%)

CYP cytochrome P450, D-AMB amphotericin B deoxylate, *IM* intramuscular, *IV* intravenous, *L-AMB* liposomal amphotericin B, *RES* Reticuloendothelial system

[a] More lipid formulations exist of amphotericin B, but these are outside the scope of this review

Pharmacokinetics provide a scientific framework for choosing the appropriate (combination of) drugs and their dosage. The clinical pharmacokinetics of antileishmanial drugs, however, remain largely unexplored [6]. The aim of this review is to give a comprehensive overview of the pharmacokinetic characteristics relating to the absorption, distribution, metabolism and excretion (ADME) of systemically administered antileishmanial drugs currently being used in the clinic as a basis to further rationalise the therapy for leishmaniasis. Albeit the pharmacokinetics of miltefosine [7] and liposomal amphotericin B (L-AMB, with focus on treatment of fungal infections [8]) have previously been reviewed, our aim was to discuss the antileishmanial drugs collectively in the context of leishmaniasis.

We have composed a summary of all pharmacokinetic studies performed, providing the reported primary and secondary pharmacokinetic parameters in overview tables. The pharmacokinetics in special patient populations relevant in treatment of leishmaniasis are described: paediatric patients, HIV co-infected patients, pregnant patients and patients with renal failure. Furthermore, potential drug–drug interactions between antileishmanial drugs, as well as between antileishmanial and antiretroviral drugs are discussed. When information in humans is lacking, in vitro and in vivo animal studies are examined.

In this review we solely focus on systemically administered drugs, as the majority of these drugs are administered in both CL and VL. Topical formulations were omitted due to its sole applicability to CL patients. The systemic drugs included in this review (Table 1) are based on the World Health Organization (WHO) guidelines on *Control of the Leishmaniases* [2]: pentavalent antimony, paromomycin, pentamidine, miltefosine and AMB. In addition to these drugs, ketoconazole has been mentioned in systemic treatment of 'new world' CL species. Given the drug's limited clinical use and the decisions by the US Food and Drug Administration (FDA) and European Medicines Agency (EMA) to suspend its oral use in skin infections due to severe hepatotoxicity [9], ketoconazole is not discussed in this review.

With this review we aim to provide a more solid pharmacokinetic basis for a scientific approach to treatment design in future clinical studies investigating (combination) treatments against leishmaniasis. In addition, our aim was to identify knowledge gaps to guide future pharmacokinetic studies in this clinical area.

2 Methods

Pharmacokinetic studies were included in this review (Tables 2, 3, 4, 5, 6, 7) if pharmacokinetic parameters were reported in addition to drug concentrations. Pharmacokinetic studies based on bio-assays were excluded due to low sensitivity and problems with potential co-measurements of the effect of metabolites. Many pharmacokinetic studies have been conducted for AMB, and for this reason we excluded studies with fewer than ten subjects or patients, studies with continuous infusion and studies on neonates <3 kg based on their limited relevance in the context of the treatment of leishmaniasis. Studies on experimental formulations were excluded for all drugs, such as a pharmacokinetic study on the experimental generic sodium stibogluconate (SSG) formulation 'Ulamina' composed of the pentachloride of antimony plus *N*-methylglucamine [10], as no records have been found of the commercialisation of this formulation.

3 Absorption, Distribution, Metabolism and Excretion (ADME) and Clinical Pharmacokinetics

3.1 Pentavalent Antimonials

Pentavalent antimonials (pentavalent Sb/Sb^{V}) have been first-line treatment against CL and VL in the majority of endemic regions for decades, though increasing drug resistance has compromised its efficacy [3, 4]. Pentavalent antimonials are administered intramuscularly (IM) or intravenously (IV) in systemic treatment of both CL and VL. It is marketed in two formulations: SSG (marketed as Pentostam®) and meglumine antimoniate (MA, marketed as Glucantime®). The Sb content in the two antimonials is different with 85 mg Sb/mL in MA and 100 mg Sb/mL in SSG. Due to structural differences in these compounds, differences in pharmacokinetics could be expected. Unless indicated otherwise, results refer to SSG, as this is the most widely studied compound. All pharmacokinetic studies used analytical methods that do not distinguish between different chemical forms of antimony (Sb^{V}, trivalent antimony Sb^{III}, etc.) [11]. The abbreviation Sb is used to refer to (total) antimony and will be used when discussing the results of the pharmacokinetic studies.

Despite being used in the clinic for decennia, the mechanism of action of Sb is not well-understood. Two main models currently exist: the pro-drug model and the active Sb^{V} model. In the active Sb^{V} model, Sb^{V} has intrinsic antileishmanial activity finally leading to the inhibition of DNA topoisomerase I [12]. According to the pro-drug model, Sb^{V} compounds are pro-drugs exerting its activity against the *Leishmania* parasite after reduction to Sb^{III} in host cells [13]. Sb^{III} finally induces apoptosis by the activation of oxidative stress and increase of intracellular Ca^{2+} [12, 14]. Multiple studies have identified an indirect effect of Sb on immune activation (overview in Mookerjee Basu et al. [15]). The most

Table 2 Pentavalent antimonials: primary and secondary pharmacokinetic parameters

Study	Patients	Weight (kg)	Daily dose	Sampling day	C_{max} (μg/mL)	C_{trough} (μg/mL)	t_{max} (h)	k_a (h^{-1})	V_d/F (L)	CL/F (L/h)	AUC (mg·h/L)	$t_{½}$ (h)
Non-compartmental												
Cruz et al. [11][a]	Cutaneous leishmaniasis patients:											
	Adults: 20 mg/kg/day	62 (56–120)	20 mg/kg, 20 days	Day 19	38.8 ± 2.1	0.198 ± 0.023	1.0 (1.0–2.0)	NA	0.30 ± 0.01[b,c]	0.106 ± 0.006[b]	AUC_{24}: 190 ± 10	$t_{½,β}$: 1.99 ± 0.08 $t_{½,24–48\ h}$: 20.6 ± 1.8
	Children: 20 mg/kg/day	15 (13–18)	20 mg/kg, 20 days	Day 19	32.7 ± 0.9	0.113 ± 0.015	0.875 (0.5–1.5)	NA	0.39 ± 0.03[b,c]	0.185 ± 0.013[b]	AUC_{24}: 111 ± 7	$t_{½,β}$: 1.48 ± 0.02
	Children: 30 mg/kg/day	17.5 (13–21)	20 mg/kg, 19 days 30 mg/kg, Day 20	Day 20	43.8 ± 2.3	0.102 ± 0.011	1.0 (1.0–1.5)	NA	0.39 ± 0.02[b,c]	0.186 ± 0.012[b]	AUC_{24}: 164 ± 10	$t_{½,β}$: 1.47 ± 0.06 $t_{½,24–48\ h}$: 25.3 ± 3.1
Zaghloul et al. [19][a]	Cutaneous leishmaniasis patients	66.4 ± 8.7	First dose 300 mg (~5 mg/kg)	Day 1	6.4 ± 1.4[d]	NA	NA	3.3[e]	239 ± 32.6[f]	13.2 ± 1.5	$AUC_{∞}$: 49.88 ± 4.43[d]	$t_{½,α}$: 0.41 ± 0.15 [g] $t_{½,β}$: 9.4 ± 1.9 [g]
			600 mg (~10 mg/kg), at least 3 weeks	NA	7.23 ± 1.58	NA	1.7 ± 0.19	1.9[e]	258 ± 44.4[f]	12.86 ± 1.58	$AUC_{∞}$: 65.4 ± 8.3	$t_{½,α}$: 1.68 ± 1.3 [g] $t_{½,β}$: 9.69 ± 2.3 [g]
Compartmental												
Al-Jaser et al. [30][a]	Cutaneous leishmaniasis patients	60–75	8–10 mg/kg, 10 days	NA	8.77 ± 0.39	NA	1.34 ± 0.09	1.71±0.15	45.7 ± 2.6	17.67 ± 1.38	37.0 ± 1.57	$t_{½,α}$: 0.48 ± 0.035 $t_{½,β}$: 1.85 ± 0.072
Chulay et al. [18]	Visceral leishmaniasis patients	47.4 ± 8.05	10 mg/kg, 30 days	Day 1	10.5 ± 1.2	0.062 ± 0.018	2	0.8[e]	0.22 ± 0.057[b]	NA	NA	$t_{½,β}$: 2.02 ± 0.25 $t_{½,γ}$: 76 ± 28

Table 2 continued

Study	Patients	Weight (kg)	Daily dose	Sampling day	C_{max} (μg/mL)	C_{trough} (μg/mL)	t_{max} (h)	k_a (h^{-1})	V_d/F (L)	CL/F (L/h)	AUC (mg·h/L)	$t_{½}$ (h)
Pamplin et al. [29][a]	Cutaneous leishmaniasis patients	NA	10 mg/kg, 10 days	NA	NA	NA	NA	1.76	NA	NA	NA	$t_{½,α}$; 0.34 ± 0.9 $t_{½,β}$; 1.72 ± 0.6 $t_{½,γ}$: 32.8 ± 3.8

Data given as either mean ± standard deviation or median (range), unless indicated otherwise

AUC area under the concentration–time curve, AUC_{24} AUC from time zero to 24 h, AUC_{∞} AUC from time zero to infinity, *CL* clearance, C_{max} peak plasma concentration, C_{trough} trough plasma concentration 24 h after dose, *F* bioavailability, k_a absorption rate constant, *NA* not available, $t_{½}$ plasma elimination half-life, $t_{½,α}$ distribution half-life, $t_{½,β}$ elimination half-life, $t_{½,γ}$ terminal elimination half-life, $t_{½\ 24\text{-}48h}$ apparent half-life between 24 and 48 h (an approximation of the γ-elimination half-life) t_{max} time to C_{max}, V_d volume of distribution

[a] Values reported as mean ± standard error of the mean

[b] Per kg

[c] $V_β$ apparent volume of distribution during the β-elimination phase

[d] Data normalized to a 600 mg dose

[e] Documented as absorption $t_{½}$

[f] V_d is reported as V_{ss}, the steady-state volume of distribution including both the central and peripheral compartment

[g] Calculated with compartmental analysis, reported as distribution half-life (indicated as $t_{½,α}$) and elimination half-life (indicated as $t_{½,β}$)

common adverse effects of treatment with pentavalent antimony are myalgia/arthralgia, gastrointestinal problems and headache [16]. In addition, serious adverse effects have been reported such as cardiomyopathy, renal failure and reversible hepatic and pancreatic abnormalities [16, 17].

3.1.1 ADME

After IM injection, Sb is absorbed quickly and the peak plasma concentration (C_{max}) is reached in between 0.5 and 2 h [11, 18–20]. Absorption half-lives ($t_{½}$) varied between 0.36 and 0.85 h [18, 19].

Highest accumulation of Sb in human volunteers, after administration of radioactively labelled (Sb^{124}) sodium antimony mercapto-succinate, was recorded in the liver > thyroid > heart [21]. A full Sb tissue distribution study in rhesus monkeys on day 55 after receiving a 21-day MA treatment showed highest Sb concentrations in the thyroid > nails > liver > gall bladder > spleen [22]. In rats, distribution at 24 h after a 21-day MA treatment was highest in the spleen > kidney > thyroid > liver [23]. No protein binding data were reported.

Sb is administered systemically in treatment of CL and several studies have investigated skin Sb distribution. Al Jaser et al. [20] identified a small delay in distribution to the skin with a time to C_{max} (t_{max}) of 2.1 h compared with ~1.5 h for whole blood [20]. Skin biopsies taken from both the CL lesion and unaffected skin from patients treated with SSG ~10 mg/kg/day for 10 days indicated no difference in Sb distribution to affected versus healthy skin (mean ± standard error of the mean [SEM]: C_{max} 5.02 ± 1.43 and 6.56 ± 2.01 μg/g, respectively) [20]. Studies in Brazilian CL patients reported higher tissue concentrations with high variability after 20 days of 10–20 mg Sb/kg/day (range 8.32–70.68 μg/g [24]) and 20 mg/kg/day (7.46 ± 7.7 μg/g [25]). The wide spread in observed Sb tissue concentrations could possibly influence Sb efficacy in treatment of CL. However, no exposure–response studies were conducted in which skin exposure was related to treatment outcome.

The prevalent view is that Sb^V derived from Sb^V-based drugs is reduced to Sb^{III} intracellularly and subsequently released at slow rates, which partially explains the slow terminal elimination phase observed in total Sb. Current pharmacokinetic studies have focused on the analysis of total Sb (Table 2), but Miekeley et al. [26] used inductively coupled plasma mass spectrometry (ICP-MS) to analyse Sb^{III} and Sb^V separately. They reported the first evidence for in vivo conversion of MA into ion species Sb^V and Sb^{III} in humans. In vitro, two locations have been identified where this bioreduction could take place: the acidic compartment of mammalian cells such as the phagolysosome in which the *Leishmania* parasite resides, or the cytosol of the parasite itself [27].

Table 3 Paromomycin: primary and secondary pharmacokinetic parameters

Study	Patients	Weight (kg)	Daily dose	Sampling day	C_{max} (μg/mL)	C_{trough} (μg/mL)	t_{max} (h)	k_a (h^{-1})	V_d/F (L)	CL/*F* (L/h)	AUC (mg·h/mL)	$t_{½}$ (h)
Compartmental												
Kanyok et al. [36]	Healthy volunteers											
	12 mg/kg	68.2±14.0	12 mg/kg (9 mg/kg base), single dose	Single dose	21.6 ± 2.3	<LLOQ	1.19 ± 0.46	6.27 ± 4.41	0.35±0.04[b,c]	7.1 ± 0.78[d]	AUC_{∞}: 86.3 ± 15.0	2.21 ± 0.17
	15 mg/kg	70.7±13.0	15 mg/kg (11 mg/kg base), single dose	Single dose	23.4 ± 3.9	<LLOQ	1.51 ± 0.40	2.65 ± 1.29	0.41 ± 0.06[b,c]	7.6 ± 1.94[d]	AUC_{∞}: 104.5 ± 26.3	2.64 ± 0.82
Kshirsagar et al. [38]	Visceral leishmaniasis patients	35.5±11.8[a]	15 mg/kg (11 mg/kg base), 21 days	Day 1	20.5 ± 7.01	4.53 ± 6.71	NA	2.11 (7.68%)[e]	15.3 (2.27%)[e]	4.06 (3.05%)[e] IIV: 30.7%	NA	2.62
				Day 21	18.3 ± 8.86	1.31 ± 4.16						

Data given as mean ± standard deviation, unless indicated otherwise

AUC area under the concentration–time curve, AUC_{24} AUC from time zero to 24 h, AUC_{∞} AUC from time zero to infinity, *CL* clearance, C_{max} peak plasma concentration, C_{trough} trough plasma concentration 24 h after dose, *F* bioavailability, *IIV* inter-individual variability, k_a absorption rate constant, *<LLOQ* below lower limit of quantitation, *NA* not available, $t_{½}$ plasma elimination half-life, t_{max} time to C_{max}, V_d volume of distribution

[a] Not provided on poster [38], but provided for 501 patients included in clinical results of trial [33]: used as proxy for 448 of these 501 patients included in population pharmacokinetic model

[b] V_{β}, apparent volume of distribution during the β-elimination phase

[c] Per kg

[d] Per 1.73 m^2, reported as 117.7 and 126.0 mL/min, converted to L/h

[e] Mean (% standard error)

Table 4 Pentamidine: primary and secondary pharmacokinetic parameters

Study	Patients	Weight (kg)	Daily dose	Sampling day	C_{max} (ng/mL)	C_{trough} (ng/mL)	t_{max} (h)	V_1/F (L)	V_{ss}/F (L)	CL/F (L/h)	AUC (ng·h/mL)	$t_{½}$ (h)
Non-compartmental												
Bronner et al. [47][a]	African trypanosomiasis patients	54 (34–66)	3.5–4.5 mg base/kg, 10 days			At 48 h:					0–48 h:	
				Day 1	813 ± 1257	14 (7–16)	~1 h[b]	NA	NA	NA	2699 ± 1364[c]	23 ± 13 (n = 7)
				Day 10	825 ± 783	78 (57–92)	~1 h[b]	NA	NA	NA	5887 ± 1881[c]	47 ± 13 (n = 9)
Bronner et al. [51][a]	African trypanosomiasis patients	63 (50–84)	3.0–4.8 mg base/kg	Single dose	393 ± 168	NA	End of infusion	NA	11,817 ± 4510	67±21	0–168 h: 2494 ± 1550	Terminal $t_{½}$: 11 ± 5[c] days
Compartmental												
Conte et al. [53]	AIDS patients/ *Pneumocystis carinii* pneumonia	62 ± 17	4.0 mg salt/kg IM	Single dose	209 ± 48	6.55 ± 3.51	0.67 ± 0.26	924 ± 404	2724 ± 1066	305 ± 81	NA	$t_{½,\alpha}$: 0.90 ± 0.18 $t_{½,\beta}$: 9.4 ± 2.0
			4.0 mg salt/kg IV	Single dose	612 ± 371	2.90 ± 1.44		140 ± 93	821 ± 535	248 ± 91		$t_{½,\alpha}$: 0.30 ± 0.22 $t_{½,\beta}$: 6.4 ± 1.3
Conte et al. [57][d]	AIDS patients/ *P. carinii* pneumonia	64 ± 8 (excluding 2 children: 5.7/20 kg)	4 mg/kg[e] Various lengths of treatment	Different	NA	NA	NA	205 ± 54	1000 ± 506	411 ± 55	NA	6.2 ± 1.2
Conte et al. [54]	AIDS patients/ *P. carinii* pneumonia	66 ± 10	3 mg/kg[e], 9–18 days	Day 1	282 ± 72[f]	2.1 ± 1.4	NA	38.2 ± 27.3	3500 ± 3800	268 ± 70	AUC_{∞}: 748 ± 211	$t_{½,\alpha}$: 1.2 ± 0.6 [g] $t_{½,\beta}$: 29 ± 25
	Volunteer haemodialysis patients	73 ± 10	3 mg/kg[e], single dose	Single dose	275 ± 184	1.1 ± 0.8	NA	218 ± 295	12,400 ± 3900	592 ± 472	578 ± 407	$t_{½,\alpha}$: 1.8 ± 0.6 [g] $t_{½,\beta}$: 72.6 ± 38.1
			4 mg/kg[e], single dose	Single dose	227 ± 110	1.7 ± 0.5	NA	218 ± 200	32,400 ± 45,300	329 ± 58	747 ± 158	$t_{½,\alpha}$: 3.5±1.6 [g] $t_{½,\beta}$: 118±119
	P. carinii pneumonia patients	80 ± 8	3–4 mg/kg[e], 12–21 days	Last dose	NA	NA	NA	NA	NA	NA	N/A	Terminal $t_{½}$: 12.0 ± 2.3 days

Table 4 continued

Study	Patients	Weight (kg)	Daily dose	Sampling day	C_{max} (ng/mL)	C_{trough} (ng/mL)	t_{max} (h)	V_1/F (L)	V_{ss}/F (L)	CL/F (L/h)	AUC (ng·h/mL)	$t_{½}$ (h)
Thomas et al. [49]	AIDS patients	60.2 (58–65)	~2.3 mg base/kg	Single dose	NA	NA	NA	26 ± 8	825 ± 458	73.6 ± 35.8	AUC_∞: 2500 ± 1700	$t_{½,\alpha}$: 5.4 ± 2.4 min $t_{½,\beta}$: 11.2 ± 7.8

Data given as either mean ± standard deviation or median (range), unless indicated otherwise

AUC area under the concentration–time curve, AUC_∞ AUC from time zero to infinity, *CL* clearance, C_{max} peak plasma concentration, C_{trough} trough plasma concentration 24 h after dose, *F* bioavailability, *IM* intramuscular, *IV* intravenous, *NA* not available, $t_{½}$ plasma elimination half-life, $t_{½,\alpha}$ distribution half-life, $t_{½,\beta}$ elimination half-life, t_{max} time to C_{max}, V_1 central volume ofdistribution, V_{ss} volume of distribution at steady state

[a] All concentrations were reported in nmol/L and were translated into ng/mL with a molecular weight of 340.42 g/mol

[b] C_{max} for most patients reached within 1 h. For 3 patients, C_{max} was noted 12–24 h after the dose [47]

[c] Patients excluded if plasma concentration substantially increased after initial decrease, if concentrations were below quantitation limit or if the terminal slope was very different

[d] Only reported for 5 adult patients without renal failure (IV)

[e] Unclear whether dose is reported as base or salt

[f] Only including patients with extensive sampling scheme

[g] In addition to reported slower distribution phase, a rapid distribution to peripheral tissues (mean 0.07–0.19 h^{-1}) was observed in the three-compartment model

Given the ten-fold higher toxicity of Sb^{III} species, the evaluation of Sb^{III} pharmacokinetics could play an important part in evaluating adverse effects and therapeutic action. Whilst the Sb^{III} content was negligible when analysing the drug in its formulation before administration, urine Sb^{III} concentrations of 111 µg/L were observed 11 days after the last MA injection. Also in monkeys, the proportion of Sb^{III} relative to total antimony increased from 5% on day 1 to 50% on day 9, making it a major Sb plasma species during the slow terminal elimination phase [22].

Renal clearance is consistently documented to be the main route of Sb excretion and the adult weight-adjusted Sb clearance of 0.086–0.144 L/h/kg was in the same range as normal adult glomerular filtration rates [11, 28]. The majority of Sb was eliminated via urine within 24 h after dosing with a short $t_{½}$ between 1.7 and 2.02 h [11, 18, 20, 28, 29]. Between 40 and 80% of total dose given was retrieved in urine within 24 h of dosing [19, 30]. The excess of the drug is excreted in nearly unaltered form in its formulation in complex with organic compound [26]. Significantly more rapid elimination could be observed in whole blood ($t_{½}$ = 3.04 h) than in lesion tissue ($t_{½}$ = 6.88 h) [20].

3.1.2 *Clinical Pharmacokinetics*

The pharmacokinetics of Sb (Table 2) administered IV or IM appeared to be similar: a two- or three-compartment model with bi-exponential elimination with short $t_{½}$of approximately 2 h and a terminal elimination phase of 1–3 days was found for both IV [29] and IM data [11, 18]. Miekeley et al. [26]—using the more sensitive ICP-MS for Sb analysis—reported an even slower terminal $t_{½}$ of >50 days, which could also be identified for monkeys (35.8 days) [22], hypothesised to be the intracellular conversion of Sb^V to Sb^{III}, and subsequent slow release [18].

C_{max} varied between 7.23 and 10.5 µg/mL for a 10 mg/kg daily dosing regimen [18, 19, 30] and was 38.8 µg/mL in adults receiving a 20 mg/kg dose daily. This non-linearity could possibly be explained by differences in formulation, as Chulay et al. [18] reported a slightly higher C_{max} after MA administration (11.2 µg/mL, n = 3) than after SSG (9.4 µg/mL, n = 2). However, interpretation is difficult due to the small sample size. Another possible explanation for these observations could be the lower clearance observed in the Colombian CL population. There were no significant differences in pharmacokinetic parameters between a single dose and multiple dosing [19]. Pharmacokinetics appeared linear as the area under the concentration–time curve (AUC) from time zero to 24 h (AUC_{24}) in children with a 50% increase in dose (20–30 mg/kg) increased 48% from 111 to 164 mg·h/L [11]. The Sb trough concentration (C_{trough}) gradually increased around four-fold during a 20- to 30-day treatment [11, 18, 28].

Table 5 Miltefosine: primary and secondary pharmacokinetic parameters

Study	Patients	Weight (kg)	Daily dose	C_{ss}[a] (μg/mL)	k_a (day^{-1})	t_{max} (h)	$V_{central}/F$ (L)	CL/F (L/day)	$V_{peripheral}/F$ (L)	Q (L/day)	AUC[b] (μg·day/mL)	$t_{½}$ (days)
Non-compartmental												
Berman [61]	NA	NA	NA	70[c]	NA	8–24	NA	NA	NA	NA	NA	150–200 h
Castro et al. [100]	Adult cutaneous leishmaniasis patients	70.84 ± 11.73	2.11 ± 0.32 mg/kg/day, 28 days	31.9 (17.2–42.4)	NA	NA	NA	NA	NA	NA	628 (213–861) 880 (427–1206)[d]	34.4 (9.5–46.15)
	Paediatric cutaneous leishmaniasis patients	26.22 ± 7.62	2.27 ± 0.16 mg/kg/day, 28 days	22.7 (17.0–29.3)	NA	NA	NA	NA	NA	NA	448 (304–583) 652 (438–832)[d]	37.1 (7.4–47.0)
Compartmental												
Dorlo et al. [70]	Cutaneous leishmaniasis patients	85 (70–113)	150 mg, 28 days	30.8 (median)	8.64 (10.1%)[e] IIV: 24.2%	NA	39.6 (4%) IIV: 18.3%[f]	3.87 (5.3%) IIV: 23.2%[f]	1.65 (12.4%)	0.0375 (22.0%)	NA	7.05 (5.45–9.10) Terminal $t_{½}$: 30.9 (30.8–31.2)
Dorlo et al. [71]	Paediatric visceral leishmaniasis patients	15 (9–23)	1.5–2.5 mg/kg, 28 days	NA	9.98 (11.5%)[g] IIV: 18.4%	NA	40.1 (4.5%)[h] IIV: 34.1%[f]	3.99 (3.5%)[h] IIV: 32.1%[f]	1.75 (8.2%)	0.0347 (18.3%)	NA	$t_{½}$ (range): 4.99–7.18 Terminal $t_{½}$: 35.5
	Adult visceral leishmaniasis patients	36 (16–58)	50–150 mg, 3–6 week									
	Cutaneous leishmaniasis patients[i]	85 (70–113)	150 mg, 28 days									

Table 5 continued

Study	Patients	Weight (kg)	Daily dose	C_{ss}[a] (μg/mL)	k_a (day^{-1})	t_{max} (h)	$V_{central}/F$ (L)	CL/F (L/day)	$V_{peripheral}/F$ (L)	Q (L/day)	AUC[b] (μg·day/mL)	$t_{½}$ (days)
Dorlo et al. [72][j]	Nepalese VL patents	40 (8–56)	Adults: >25 kg: 100 mg, ≤25 kg: 50 mg, 28 days Children: 2.5 mg/kg, to nearest 10 mg, 28 days	35.3 (11.6–120)	NA	NA	38.5 (4.5%)[h] IIV: 31.6%[f]	3.69 (3.4%)[h] IIV: 35.1%[f]	1.69 (8.6%)	0.0316 (16.6%)	724 (265–2260) 1140 (340–4200)[d]	6.26 (4.18–9.27) Terminal $t_{½}$: 48.9 (48.6–51.0)

Data given as either median (range) or mean (coefficient of variation %), unless indicated otherwise

Trough concentration (C_{trough}) not available for miltefosine

AUC area under the concentration–time curve, *CL* clearance, C_{ss} steady-state concentration, *F* bioavailability, *IIV* inter-individual variability, k_a absorption rate constant, *NA* not available, *Q* intercompartmental clearance, t_{max} time to C_{max} within one dosing interval, *V* volume of distribution, $t_{½}$ plasma elimination half-life, $V_{central}$ volume of distribution of the central compartment, $V_{peripheral}$ volume of distribution of the peripheral compartment, *VL* visceral leishmaniasis

[a] Miltefosine accumulates during treatment and reaches C_{ss} during the last week of treatment

[b] AUC_{D28} (AUC from start to end of treatment) unless indicated otherwise

[c] Unclear whether this is the mean C_{ss} or the maximum C_{ss}

[d] AUC from start of treatment to infinity (AUC_{∞})

[e] Reported as 0.36 h^{-1}

[f] IIV of clearance and volume of central compartment were correlated

[g] Reported as 0.416 h^{-1}

[h] Parameter scaled to a standardised fat-free mass of 53 kg. This corresponds to a theoretical weight of 70 kg

[i] Same patients as described in Dorlo et al. [70]

[j] Parameters estimated with data of Nepalese VL patient cohort and additional information on previously described cohorts (Dorlo et al. [70]/Dorlo et al. [71])

Table 6 Amphotericin B: primary and secondary pharmacokinetic parameters based on non-compartmental analyses and individual-based compartmental models

Study	Patients	Weight (kg)	Daily dose	Sampling day	C_{max} (μg/mL)	V_d (L/kg)	V_{ss} (L/kg)	CL (mL/h/kg)	AUC[a] (μg·h/mL)	$t_{½}$ (h)
L-AMB										
Gubbins et al. [86]	Peripheral stem cell transplant (PSCT) patients	71.7 ± 13.3	1.0 mg/kg, 15 days	Day 1	8.1 ± 4.2	0.19 ± 0.14	NA	15.6 ± 10.8	112.2 ± 75.3[b]	9.7 ± 3.1
				Day 7	13.5 ± 9.1	0.16 ± 0.20		10.6 ± 10.6	333.7 ± 548[b]	13.0 ± 11.8
		83.9 ± 26.1	7.5 mg/kg weekly, 2 weeks	Day 1–7	95.5 ± 39.9	0.17 ± 0.20	NA	8.9 ± 11.0	1887 ± 1344[b]	19.2 ± 1.8
				Day 7–15	52.3 ± 19.1	0.47 ± 0.22		21.6 ± 8.8	384.7 ± 126.3[b]	36.4 ± 24.4
		87.5 ± 27.1	15 mg/kg, single dose	Day 1–8	206.3 ± 89.1	0.28 ± 0.22	NA	5.6 ± 4.4	5019 ± 4199[b]	32.8 ± 12.2
Walsh et al. [89]	Neutropenic patients	NA	1.0 mg/kg, various durations	Day 1	NA	0.58 ± 0.40	0.44 ± 0.27	39 ± 22	32 ± 15[b]	10.7 ± 6.4
				Last day		0.16 ± 0.04	0.14 ± 0.05	17 ± 6	66 ± 21[b]	7.0 ± 2.1
			2.5 mg/kg, various durations	Day 1	NA	0.69 ± 0.85	0.40 ± 0.37	51 ± 44	71 ± 36[b]	8.1 ± 2.3
				Last day		0.18 ± 0.13	0.16 ± 0.09	22 ± 15	213 ± 196[b]	6.3 ± 2.0
			5.0 mg/kg, various durations	Day 1	NA	0.22 ± 0.17	0.16 ± 0.10	21 ± 14	294 ± 102[b]	6.4 ± 2.1
				Last day		0.11 ± 0.08	0.10 ± 0.07	11 ± 6	621 ± 371[b]	6.8 ± 2.1
			7.5 mg/kg, various durations	Day 1	NA	0.26 ± 0.15	0.18 ± 0.10	25 ± 22	534 ± 429[b]	8.5 ± 3.9
				Last day		0.20 ± 0.07	0.17 ± 0.05	20 ± 7	417 ± 155[b]	6.9 ± 0.9
Walsh et al. [88]	Immunocompromised patients with invasive fungal infections	NA	7.5 mg/kg, various durations	Day 1	75.9 ± 58.4	0.22 ± 0.18	0.24 ± 0.18	23 ± 14	692 ± 834	6.8 ± 1.9
				Last 7	115.1 ± 104.9	0.14 ± 0.10	0.14 ± 0.11	15 ± 11	1333 ± 2153	6.0 ± 0.8
			10.0 mg/kg. various durations	Day 1	119.6 ± 69.8	0.23 ± 0.24	0.22 ± 0.23	18 ± 19	1062 ± 971	8.0 ± 1.5
				Last 7	164.7 ± 119.7	0.16 ± 0.17	0.14 ± 0.14	12 ± 12	1919 ± 2056	8.4 ± 2.6
			12.5 mg/kg. various durations	Day 1	116.3 ± 47.8	0.18 ± 0.13	0.16 ± 0.07	16 ± 6	860 ± 390	7.1 ± 3.5
				Last 7	147.4 ± 69.2	0.16 ± 0.10	0.13 ± 0.08	13 ± 7	1168 ± 991	8.2 ± 2.5
			15.0 mg/kg. various durations	Day 1	105.1 ± 30.9	0.33 ± 0.12	0.23 ± 0.09	25 ± 8	554 ± 30.9	9.0 ± 3.1
				Last 7	178.6 ± 49.0	0.18 ± 0.09	0.14 ± 0.06	14 ± 7	1152 ± 617	9.0 ± 0.9
L-AMB + D-AMB										

Table 6 continued

Study	Patients	Weight (kg)	Daily dose	Sampling day	C_{max} (μg/mL)	V_d (L/kg)	V_{ss} (L/kg)	CL (mL/h/kg)	AUC[a] (μg·h/mL)	$t_{½}$ (h)
Bekersky et al. [87]	Healthy volunteers									
	L-AMB	79 ± 11	2 mg/kg, single dose	Single dose	22.9 ± 10	1.63 ± 0.88	0.774 ± 0.55	9.7 ± 5.4	171 ± 126 288 ± 209[b]	$t_{½,α}$: 0.56 ± 0.48 $t_{½,β}$: 6.0 ± 2.1 $t_{½,γ}$: 152 ± 116
	D-AMB	77 ± 9	0.6 mg/kg, single dose	Single dose	1.43 ± 0.2	2.34 ± 0.20	1.81 ± 0.24	13.1 ± 2.0	13.9 ± 2.0 46.6 ± 7.2[b]	$t_{½,α}$: 0.17 ± 0.14 $t_{½,β}$: 6.8 ± 1.6 $t_{½,γ}$: 127 ± 30
Heinemann et al. [95]	Critically ill patients									
	L-AMB	72 (57–85)	1.2–4.2 mg/kg	Steady state	14.4 (6.4–89.0)	0.42 (0.055–0.93)	NA	0.363 (0.036–0.942) mL/min	171 (53.1–1380)	$t_{½,α}$: 1.65 (1.25–5.22) $t_{½,β}$: 13.1 (8.7–41.4)
	D-AMB	70 (50–120)	1.0 mg/kg	Steady state	1.70 (1.45–2.07)	2.41 (1.12–4.32)	NA	1.20 (0.59–1.91) mL/min	18.65 (9.73–28.30)	$t_{½,β}$: 26.8 (9.9–37.0)
D-AMB										
Ayestarán et al. [133]	Neutropenic patients	64.4 (mean)	0.7–1 mg/kg	Day 1	2.83 ± 1.17	NA	0.56 ± 0.15	33.0 ± 14.3	29.0 ± 15.5	$t_{½,α}$: 0.64 ± 0.24 $t_{½,β}$: 15.2 ± 5.25
Benson and Nahata [134]	Paediatric patients	21.6 ± 13.3	0.25–1.5 mg/kg	Various	1.64 (0.7–10.0)	0.71 ± 0.23	NA	21.0 ± 1.8	NA	18.1 ± 6.6
Kan et al. [135]	Healthy volunteers	74.2 (55–87)	0.1 mg/kg	Various	0.551 ± 0.025	NA	0.50 ± 0.05	10 ± 1	3.9 ± 0.43	30.8 ± 4.1
			0.25 mg/kg	Various	0.984 ± 0.056	NA	0.74 ± 0.13	10 ± 1	8.7 ± 0.76	50.0 ± 11.3
Koren et al. [102]	Infants/children	NA	0.5–1 mg/kg	Various	NA	0.378	NA	26 ± 5	NA	9.93 ± 1.5

Data given as either mean ± standard deviation or median (range)

Trough plasma concentration not included as it was only documented for Bekersky et al. [87]

AUC area under the concentration–time curve, *CL* clearance, C_{max} peak plasma concentration, *D-AMB* amphotericin B deoxycholate, *L-AMB* liposomal amphotericin B, *NA* not available, $t_{½}$ plasma half-life, $t_{½,α}$ distribution half-life, $t_{½,β}$ elimination half-life, $t_{½,γ}$ terminal half-life, V_d volume of distribution, V_{ss} volume of distribution at steady state

[a] AUC from zero to 24 h after dose (AUC_{24}), unless indicated otherwise

[b] AUC from zero to infinity (AUC_{∞})

Table 7 Amphotericin B: primary and secondary pharmacokinetic parameters derived from population-based compartmental studies

Study	Patients	Weight (kg)	Daily dose	C_{max} (μg/mL)	C_{trough} (μg/mL)	$V_{central}$ (L)	CL (L/h)	$V_{peripheral}$ (L)	Q (L/h)	AUC (μg·h/mL)	$t_{½}$ (h)
Compartmental (population based)											
Hong et al. [92]	Paediatric patients with malignant disease (L-AMB)	28.8 (mean)	0.8–5.9 mg/kg	NA	NA	3.12 (40%)[a] IOV: 56%	0.44 (27%)[a] IIV: 10% IOV: 46%	18.0 (40%) IIV: 74%	0.73 (18%) IIV: 77%	NA	Terminal $t_{½}$: 59.4 ± 36.5
Hope et al. [90]	Patients with suspected invasive fungal infection (L-AMB)	68 (mean)	Intermittent: 10 mg/kg (day 1), 5 mg/kg (day 3/6) Conventional: 3 mg/kg, 14 days	NA	NA	20.6 ± 15.3	1.6 ± 0.85	NA	NA	NA	NA
Würthwein et al. [91]	Allogeneic haematopoietic stem cell recipients (L-AMB)	72 (44–105)	3 mg/kg, median 10 days	18.0 ± 8.6[b]	6.5 ± 5.8[b]	19.2 (9%) IIV: 38%	1.22 (16%) IIV: 64%	52.8 (29%) IIV: 84%	2.18 (13%) IIV: 47%	228 ± 159[b]	Terminal $t_{½}$: 54.3
Nath et al. [136][c]	Children with malignant disease (D-AMB)	23.3 ± 1.3	1 mg/kg, up to 8 days	NA	NA	8.51 (38%)	0.79 (29%)	NA	NA	NA	$t_{½,λ1}$: 1.46 ± 0.33 $t_{½,λ2}$: 26.4 ± 11.6
Ohata et al. [93]	Patients with invasive fungal infection (L-AMB)	27.1 ± 14.1	2.5 mg/kg loading dose Subsequently 1.0 or 5.0 mg/kg	18.2 ± 11[d] (observed) 17.3 ± 7.6[d] (predicted)	NA	3.43 (19%)[e] IIV: 100.2%	0.255 (16%)[e] IIV: 104.4%	6.97 (29%)[e] IIV: 238.5%	0.661 (45%)	NA	NA
Lestner et al. [94]	Immunocompromised children (L-AMB)	26.9 ± 14.0	2.5, 5.0, 7.5 or 10.0 mg/kg	NA	NA	Initial[f]: 10.7 (14.3%) Final[f]: 2.3 (42.1%)	0.67 L/h/70 kg	NA	NA	NA	NA

Data given as either mean ± standard deviation, median (range) or mean (coefficient of variation %), unless indicated otherwise

AUC area under the concentration–time curve, *CL* clearance, C_{max} peak plasma concentration, C_{trough} trough plasma concentration 24 h after dose, *D-AMB* amphotericin B deoxycholate, *IIV* inter-individual variability, *IOV* inter-occasion variability, *L-AMB* liposomal amphotericin B, *NA* not available, Q intercompartmental clearance, $t_{½}$ plasma elimination half-life, $t_{½,λ1}$ distributional half-life, $t_{½,λ2}$ elimination half-life, $V_{central}$ volume of the central compartment, $V_{peripheral}$ volume of the peripheral compartment

[a] Parameter scaled to a standardised weight of 21 kg

[b] At steady state, exact definitions of C_{max} and minimum concentration (C_{min}) not provided in publication

[c] Posterior Bayesian estimates of the pharmacokinetic parameters for D-AMB, based on model including both D-AMB data and lipid emulsion data

[d] After single dose of 2.5 mg/kg daily

[e] Parameter scaled to a standardised weight of 23 kg

[f] A decrease was identified in $V_{central}$ between the first and last day of treatment; these were estimated separately

As mentioned previously, all pharmacokinetic studies used analytical methods that do not distinguish between different chemical forms of antimony (Sb^{III}, Sb^{V}, etc.) [11]. Sb^{III} is assumed to be the active component in Sb treatment in the pro-drug model. As only a small proportion of total Sb consists of Sb^{III}, total Sb might not accurately reflect the pharmacokinetics of antimonials, especially as inter-patient differences could be expected in the intracellular reduction to Sb^{III}. This accentuates the relevance of studying the intracellular pharmacokinetics of Sb.

3.2 Paromomycin

Paromomycin, an aminoglycoside also known as aminosidine, is a highly hydrophilic and lipid insoluble antibiotic drug. Paromomycin is active against Gram-positive and Gram-negative bacteria, including *Mycobacterium tuberculosis*, and against some protozoa, including the *Leishmania* parasite. It is administered IM both as a monotherapy and as a shorter combination treatment together with SSG (reviewed in Davidson et al. [31]). Paromomycin is formulated as the salt paromomycin sulphate, of which approximately 75% consists of the base although sulphate salt contents vary per batch [32].

Paromomycin inhibits protozoan protein synthesis by binding to the 30S ribosomal subunit resulting in the accumulation of abnormal 30S–50S ribosomal complexes and finally causing cell death. In the phase III clinical trial in Indian VL patients, the most common adverse effects were injection-site pain (55%), rise in hepatic transaminases (6%), ototoxicity (2%) and renal dysfunction (1%) [33].

3.2.1 ADME

Paromomycin is generally documented to be very poorly absorbed after oral administration [34, 35]. However, like other aminoglycosides, it is rapidly absorbed from IM injection sites and its absorption is nearly 100% [32]. The t_{max} is reached within 1 or 2 h after IM injection [33, 36, 37]. The absorption rate constant (k_a) was found to be 2.11–2.65 h^{-1} for a 15 mg/kg dose, but 6.27 h^{-1} for the 12 mg/kg dosing [36, 38], though variation in the latter is large [standard deviation (SD) of 4.41 h^{-1}].

At physiological pH, paromomycin is polar, which limits its distribution towards the intracellular fluids and tissues. In dogs, protein binding is limited to 4% [39], similar to other aminoglycosides' binding in human serum [40]. Protein binding of paromomycin in humans is mostly stated to be negligible, though one study reported 33% protein-bound paromomycin [41]. The one-compartmental population pharmacokinetic model with low volume of distribution (V_d) of only 15.3 L that has been reported [38] is consistent with limited distribution and protein binding.

Paromomycin is not metabolised and is primarily excreted unchanged via glomerular filtration in the kidneys [32, 41, 42], with a renal clearance of 101.0 ± 16.5 mL/min/1.73 m^2 [36]. Elimination of paromomycin is fast: within 4 h over 50% of the dose could be detected in urine [36]. The $t_{½}$ is between 2 and 3 h [36, 38].

3.2.2 Clinical Pharmacokinetics

Two studies were performed on paromomycin pharmacokinetics (Table 3): one in healthy volunteers and one in a large population of Indian VL patients. Primary and secondary pharmacokinetic parameters were comparable between the two studies, indicating there were no specific disease effects of VL on the pharmacokinetics of paromomycin [36, 38].

V_d was directly proportional to weight and was around 0.4 L/kg for both studies [37, 39]. In the two studies, C_{max} was comparable (22–23 vs. 18–21 μg/mL), without differences between males and females. A similar C_{max} (mean ± SD) was observed in healthy Sudanese subjects (19.5 ± 7.6 μg/mL) [43]. Sudanese VL patients, however, had a much lower C_{max} of 5.6 ± 4.2 μg/mL at 15 mg/kg and 7.8 ± 4.9 μg/mL at 20 mg/kg [37]. This could imply differences in paromomycin pharmacokinetics in VL patients between regions, but interpretation is hampered by the small sample size in the Sudanese VL population ($n = 9$).

There were no significant differences in dose-adjusted AUC from time zero until infinity (AUC_∞) between dosing groups (12 mg/kg: 9.29 ± 1.52 mg·h/L per mg/kg; 15 mg/kg: 9.29 ± 2.2 mg·h/L per mg/kg), indicating linear pharmacokinetics at these dose levels [36]. There was no evidence of drug accumulation or induction of metabolism upon multiple dosing [33]. C_{trough}, however, declined from 4.53 ± 6.71 μg/mL on day 1 to 1.31 ± 4.16 μg/mL on day 21, but with high variation [33].

The site of action of paromomycin is intracellular and resistance of parasites against paromomycin was found to be related to decreased drug uptake in resistant compared with wild-type strains [44]. This affirms the importance of evaluating intracellular pharmacokinetics of paromomycin in future pharmacokinetic studies.

3.3 Pentamidine

Pentamidine is a synthetic derivative of amidine, which was used to treat refractory VL in India in the 1980s. Since then it has been used as a second-line therapy against leishmaniasis, but has mainly been administered for treatment of sleeping sickness and *Pneumocystis carinii* (now known as *P. jerovicii*) infections in AIDS patients. The drug is given by IM or, preferably, IV administration. In

the past, two lyophilised salts of pentamidine were marketed. However, since the 1990 s the production of pentamidine dimesylate ceased while pentamidine isethionate remained, which contains 1 g of base per 1.74 g of salt. As both formulations are salts dissolved in water, no differences were expected in their pharmacokinetics.

The mechanism of action of pentamidine is unclear, but the mitochondrion was found to be an important target of pentamidine action [45]. The use of pentamidine in treatment against leishmaniasis is mainly limited by its severe adverse effects: diabetes mellitus, severe hypoglycaemia, shock, myocarditis and renal toxicity [2].

3.3.1 ADME

Due to the two strongly basic amidine groups, oral bioavailability of pentamidine is low [46]. Therefore, pentamidine is administered IV or IM in treatment of leishmaniasis. The t_{max} after IM injection is approximately 1 h [47].

The distribution of pentamidine was studied in biopsies of 22 deceased AIDS patients [48]. Organs with the highest accumulated pentamidine concentrations were the kidney, liver, spleen and adrenal glands. Radiolabelled pentamidine in humans is rapidly taken up by the liver: 2.5 h after commencement of IV infusion, 65% of the drug could be traced to the liver [49]. Pentamidine seemed to be excreted in bile, but the release from the liver is slow: 99% of the absorbed pentamidine in the liver is still present 24 h after IV infusion [49]. Pentamidine is approximately 70% protein bound.

Pentamidine was extensively metabolised in isolated perfused rat liver [50]. In vitro cytochrome P450 (CYP) enzymes CYP2D6 and CYP1A1 were responsible for pentamidine metabolism in human liver microsomes [51]. Involvement of CYP1A1 in pentamidine metabolism was later confirmed in human liver microsomes, with additional involvement of CYP3A5 and CYP4A11, but involvement of CYP2D6 could not be identified [52]. No data could be found on pentamidine metabolites in humans [52].

Multiple studies found a low urinary excretion of pentamidine of between 2.1 and 5.5% or below 20% in the first 24 h after infusion [49, 53–55]. Faecal excretion was found to be only one-third of the amount excreted in urine [56].

3.3.2 Clinical Pharmacokinetics

Pentamidine pharmacokinetics are best described by two- or three-compartment models (Table 4). A rapid distribution phase was observed with a sharp 32% plasma concentration decrease within 10 min after end of infusion ($t_{½} \sim 5$ min) [51, 54].

Pentamidine pharmacokinetics have most extensively been studied in the 1980s and 1990s in heterogeneous patient populations. As can be seen from Electronic Supplementary Material Table 3, included patients are often a mixture of male/female, child/adult, with/without renal failure, dialysis/no dialysis and AIDS patients/non-AIDS patients, with different dosages and sampling schemes. This possibly explains the wide variability in reported pharmacokinetic parameters. Regardless of the high variability, a consistently large V_d was observed, consistent with 70% protein binding. There is a large variability in the documented elimination $t_{½}$ of pentamidine, but a consistent 11- to 12-day terminal $t_{½}$ was found [51, 54] (Table 4). Pentamidine accumulates during treatment [47, 54, 57, 58] and pre-dose C_{trough} levels increased from 14 to 78 ng/mL during a 10-day once-daily treatment [47].

It is widely assumed that the *Leishmania* infection inhibits hepatic drug metabolism, which was found to be mediated by nitric oxide in hamsters [59]. This could possibly affect pentamidine exposure in VL patients, as pentamidine is metabolised by CYP enzymes. However, to our knowledge, the pharmacokinetics of pentamidine have never been investigated in VL patients.

3.4 Miltefosine

Miltefosine is an alkylphosphocholine drug with a polar head and hydrophobic tail and a critical micelle concentration of approximately 20 μg/mL (50 μmol/L) [60]. Though originally developed as an anti-cancer drug, it has been licensed since 2002 in India for VL treatment and since 2004 in Germany for treatment of CL.

No definite mode of action is determined for miltefosine, but multiple hypotheses have emerged, such as induction of apoptosis, disturbance of lipid-dependent cell signalling pathways, alteration of membrane composition and immunomodulatory effects [7]. Miltefosine is orally administered in standard treatment of 2.5 mg/kg daily for 28 days and this is well-tolerated with mainly gastrointestinal adverse effects.

3.4.1 ADME

Miltefosine is slowly absorbed upon oral administration. The k_a is approximately 9 $days^{-1}$, which corresponds to an absorption $t_{½}$ of $\sim$2 h. The t_{max} was reported to be between 8 and 24 h [61]. In East-African VL patients, absorption appeared to be even slower, indicating a possible disease effect on the absorption of miltefosine (Dorlo et al., unpublished data). Bioavailability in rats and dogs was found to be 82 and 94%, respectively [7]. No data are available in humans, due to the haemolytic activity of miltefosine after IV infusion [62, 63].

Pre-clinical in vivo studies in mice and rats indicated a wide distribution of miltefosine and uptake in a range of different tissues. In rats, [^{14}C]-radioactively labelled miltefosine was predominantly found in the kidney > intestinal mucosa > liver > spleen [64]. Another study in rats showed similar distribution patterns after 18 days of oral miltefosine administration (kidney > adrenal > skin > spleen > small intestines) [65]. Radiolabelled miltefosine oral administration in mice resulted in accumulation in the kidney > liver > lung [66].

In humans, plasma protein binding was 96–98%, of which 97% bound to albumin [62]. Miltefosine accumulated in peripheral blood mononuclear cells (PBMCs), with an approximately two-fold higher PBMC than plasma concentration [67]. A 0.4 μg/mL miltefosine cerebrospinal fluid (CSF) concentration was measured after 5 days of miltefosine treatment in patients with granulomatous amoebic encephalitis, suggesting a 2–4% miltefosine passage across the blood–brain barrier, although integrity of the barrier could not be guaranteed [68].

An in vitro evaluation of 15 different CYP enzymes revealed no oxidative metabolism of miltefosine [7, 61] and no CYP3A isoenzyme induction was observed in vivo in rats [61]. Instead, miltefosine is most probably metabolised intracellularly by phospholipase D [64, 66]. No metabolic conversion of miltefosine was observed by phospholipases A and B [64], and metabolism by phospholipase C is still debated [64, 66]. After IV infusion with radioactive miltefosine in mice, most radioactivity in the liver was attributable to unchanged miltefosine (63%), with the main breakdown product being choline (32%), with low levels of phosphocholine (3%) and 1,2-diacylphosphatidylcholine (2%) [66].

The breakdown products of miltefosine are abundant endogenous compounds and are therefore difficult to quantify, e.g. choline is involved in the biosynthesis of cell membranes. There is little excretion of unchanged miltefosine; excretion of miltefosine in urine accounts for only <0.2% of the administered dose at day 23 of treatment [61]. Faecal elimination has not been evaluated in humans, but slow faecal elimination of 10% of total miltefosine excretion has been reported in Beagle dogs [69].

3.4.2 Clinical Pharmacokinetics

In contrast to older antileishmanial drugs, the pharmacokinetics of miltefosine have been studied more intensively (Table 5). The first reported population pharmacokinetic model of miltefosine identified a long terminal elimination phase with a $t_{½}$ of 31 days [70], in addition to the initially reported 7-day elimination $t_{½}$ [61]. Due to this long $t_{½}$, miltefosine accumulates during treatment to finally reach steady-state concentrations approximately in the last week of the 28-day treatment. In a more extensive population pharmacokinetic model, including data on both adult and paediatric patients with CL or VL, differences between patients in V_d and clearance could best be described by allometrically scaling these parameters by fat-free mass [71]. A lower exposure was found for children than for adults while receiving the same 2.5 mg/kg dose (see Sect. 4.1).

To date, only one study has been published on the relationship between exposure and response in antileishmanial therapies [72]. A 1-day decrease in the time the miltefosine plasma concentration was above the $10 \times EC_{50}$ (mean half-maximal effective concentration), compared with the median of 30 days, was associated with a 1.08-fold increase in odds of treatment failure in VL [72]. Miltefosine has been found to accumulate intracellularly in PBMCs, which could influence miltefosine exposure at its site of action, though no significant correlation could be identified with treatment outcome in a non-compartmental analysis [67].

3.5 Amphotericin B

AMB is a polyene antifungal, is poorly soluble in water and has a high affinity for sterol-containing membranes. The two main formulations are AMB deoxylate (D-AMB) and liposome encapsulated AMB (L-AMB). D-AMB was developed in the 1950 s and has been widely administered as an antifungal drug for the treatment of invasive fungal infections, but its dose-limiting nephrotoxicity and hypokalaemia hampers its use in the clinic. The lipid formulation L-AMB, incorporating AMB in a liposome bilayer, significantly reduced its renal toxicity and infusion-related toxicity. AMB binds to ergosterol in the cell membrane, subsequently leading to pore formation, fluid leakage and cell death. L-AMB adverse effects are mild infusion reactions and transient nephrotoxicity or thrombocytopenia.

Other lipid-based formulations of AMB exist such as AMB lipid complex (ABLC; Abelcet®) or AMB colloidal dispersion (ABCD; Amphocil™/Amphotec®). In this review we only focus on L-AMB (AmBisome®), since this is the most widely used lipid AMB formulation in leishmaniasis. Any findings regarding L-AMB cannot be extrapolated to other lipid formulations of AMB, as substantial differences exist in pharmacokinetic parameters between these formulations [8, 73].

AMB exists in different forms in the plasma: protein-bound AMB, free AMB and, upon L-AMB administration,

also liposome-associated AMB. To date, all but one of the pharmacokinetic studies only determined the total AMB concentration after destruction of the liposome with organic solvent and subsequent release of AMB. If not clarified otherwise, the abbreviation AMB refers to total AMB.

3.5.1 ADME

AMB is poorly absorbed after oral administration, due to the hydrophobicity of its polyene structure. Daily dosages of 2–5 g resulted in (subtherapeutic) systemic concentrations of below 0.5 μg/mL (reviewed in Janknegt et al. [74]).

AMB is highly protein bound (>90%) [75]. In vitro binding in human plasma, determined by ultrafiltration, showed that 95–99.5% of AMB was bound in plasma, with increasing percentages bound with increasing AMB concentrations [76].

Interestingly, a physiologically based pharmacokinetic model has recently been developed describing the biodistribution of AMB in tissues of mouse, rat and human [77]. To describe the data well, a saturable uptake of AMB in reticuloendothelial system organs, such as the VL target sites spleen and liver, was required. Predicted human tissue data were in good correspondence with autopsy data from patients who received L-AMB therapy [78]. In three autopsy cases, highest AMB concentrations (after a total dose of 820–3428 mg) were observed in the liver (92.8–291 μg/g) and spleen (150–291 μg/g), with lower concentrations in the kidney, thyroid, bone marrow and lung (<50 μg/g) [78]. Of the administered dose, 13.9–22.5% could be recovered from the liver [78]. This was in line with a larger autopsy study with seven L-AMB treated patients, where highest concentrations were found in the liver (102.81 ± 68.72 μg/g) and spleen (60.32 ± 29.75 μg/g) [79]. CSF levels were approximately 1000-fold lower than concurrent serum levels [80]. Similar distribution patterns were observed after treatment with D-AMB [81], with highest accumulation in liver (up to 188 μg/g) and spleen (up to 190 μg/g) [81]. In total, 14–41% of the administered dose could be recovered from the liver (with a total maximum recovery of 51%) [81].

The same distribution (spleen and liver > kidneys > lungs) was also found in mice [82, 83]. AMB concentrations were significantly lower in the liver and spleen of VL-infected mice than in non-infected mice, hypothesised to be due to a loss in phagocytic activity in infected macrophages [84]. Disruption of normal liver function in VL might thus affect AMB exposure in VL patients.

D-AMB skin concentrations in rats were 30–50% of plasma concentrations and show a decrease over time parallel to these plasma concentrations [85]. Upon L-AMB administration, buccal mucosal AMB concentrations rise to concentrations 6–47 times higher than plasma concentrations [86].

Metabolism of AMB has not been well-studied and metabolites have up to now not been identified [74]. Preclinical studies reported that AMB is eliminated from the circulation by the urinary and biliary tract and by the reticuloendothelial system, the latter of which is also responsible for the clearance of L-AMB from the circulation (reviewed in Gershkovich et al. [84]). One week after a single dose, urinary excretion of unchanged AMB was 20.6 and 4.5% for D-AMB- and L-AMB-treated subjects, respectively [87]. During the same period, faecal excretion was 42.5% for D-AMB-treated subjects but only 4% for subjects treated with L-AMB. Possible explanations for the decrease in excretion of unchanged AMB in the liposomal formulation could either be a change in distribution of the AMB, prolongation of its residence time or increased metabolism.

3.5.2 Clinical Pharmacokinetics

The pharmacokinetics of L-AMB, best described by a two- or three-compartment model, have been studied in a wide range of dosages (Tables 6, 7), but has never been evaluated in leishmaniasis patients.

Variability (coefficient of variation [CV%]) in pharmacokinetic parameters was much higher for L-AMB than for D-AMB (AUC_{24} CV% of 73.4 and 14.4%, respectively) [87]. High variability in AMB exposure could potentially be caused by differences in the uptake of liposomes into non-blood compartments, or differences in drug release from the carrier liposomes. Interestingly, variability in exposure decreased with higher dosages, e.g. C_{max} CV% decreased from 91 to 27% with increased dosing from 7.5 to 15 mg/kg, respectively [88].

Linear pharmacokinetics were reported up to a 7.5 mg/kg dose. At higher dosages, time-dependent non-linear L-AMB pharmacokinetics have been described [88, 89]. Evaluating L-AMB dosages of 7.5–15.0 mg/kg, the highest C_{max} and AUC levels were reached at 10 mg/kg, implying that (alternative) elimination mechanisms are induced or activated above this concentration [88]. Possibly, the uptake by the reticuloendothelial system is enhanced, which would simultaneously explain the high AMB concentration in the liver, spleen and bone marrow [88].

Considering these non-linearities and the high variability in pharmacokinetic parameters between patients, a non-compartmental analysis or individual-based compartmental analysis would not be appropriate to capture the pharmacokinetic profile of L-AMB. Five multi-

compartmental population pharmacokinetic models have been developed for L-AMB [90–94]. The median weight in these studies varies widely (Electronic Supplementary Material Table 5), since multiple studies only included paediatric patients [92, 93]. Interestingly, a recent study reported a decrease in the V_d over time during treatment [94]. Furthermore, body weight has been identified as a covariate on clearance and V_d in most modelling studies [90, 92–94], often allometrically scaled [92, 94]

For most patients, C_{trough} values increased ~2.6-fold following multiple administrations, but for a portion of patients the increase was above ten-fold (exact treatment duration not reported) [93]. Walsh et al. [89] did not find an increase in C_{trough} after repeated dosing.

Encapsulation of AMB in liposomes alters the pharmacokinetics of the drug. A lower clearance and a lower V_d was reported for L-AMB compared to D-AMB [87, 95]. The C_{max} (mean ± SD) of unbound AMB was significantly lower for patients treated with 2 mg/kg of L-AMB (0.016 ± 0.004 μg/mL) than for patients treated with 0.6 mg/kg of D-AMB (0.060 ± 0.01 μg/mL) [76], explaining the decrease in adverse effects after L-AMB administration compared with D-AMB. Unbound AMB elimination was biphasic with a longer $t_{½}$ than total AMB (initial $t_{½}$ of 7.7 ± 2.8 h, terminal $t_{½}$ of 467 ± 372 h [76]).

All AMB pharmacokinetic studies conducted were performed in often immunosuppressed patients with fungal infections and no study has been conducted in leishmaniasis patients to date. As the spleen and liver physiology is severely damaged in VL, the uptake of L-AMB by the reticuloendothelial system might be altered, possibly changing the pharmacokinetics of AMB in VL patients. Furthermore, AMB pharmacokinetics have only been evaluated in plasma. Analysing the intracellular AMB pharmacokinetics might give more reliable information on the AMB exposure of the parasite at the site of action.

4 Specific Patient Populations

4.1 Paediatric Patients

Evaluation of the pharmacokinetics of antileishmanial drugs in the paediatric patient population is of particular importance, since 45% of the global leishmaniasis incidence consists of children under the age of 15 years old [96]. However, in the clinical development of antileishmanial drugs, pharmacokinetic studies in children have often been omitted. Children mostly receive the same mg/kg dosing regimen as adults, although it is generally accepted that this leads to lower exposure in children as clearance and V_d are allometrically scaled by weight or fat-free mass [97]. For Sb, paromomycin, miltefosine and AMB, additional studies have been performed to gain more insight into the pharmacokinetics in children and to rationalise dosing in this vulnerable patient population. However, while differences in exposure between adult and paediatric patients were observed for Sb, miltefosine and AMB, specific paediatric dosages are currently only clinically being evaluated for miltefosine.

Children are relatively underexposed to miltefosine in comparison with adults (Sect. 3.5) and have a higher risk of relapse [71, 72, 98–100]. With a conventional linear 28-day 2.5 mg/kg daily dosing, only 71.4% of children reached an AUC from day zero to day 28 of treatment (AUC_{D28}) of 412 μg day/mL, while 90% of adults reached this threshold [71]. Simulating a 28-day allometric dose regimen, where low-weight patients would receive a higher mg/kg daily dose, 95.6 and 97.3% of adults and children reached an AUC_{D28} of 412 μg day/mL [71]. This allometric dose is currently being evaluated in paediatric VL patients aged 4–12 years old in Kenya and Uganda (NCT02431143 [137]), and paediatric post-kala-azar dermal leishmaniasis patients younger than 18 years old in Bangladesh (NCT02193022 [138]).

L-AMB pharmacokinetics have been characterised in paediatric patients in two population pharmacokinetic studies. Simulating different dosing regimens from 1 to 12.5 mg/kg daily for patients ranging 10–70 kg in weight, Hong et al. [92] reported that children under 20 kg would require a higher mg/kg dose to achieve comparable steady-state C_{max} levels. However, weight could not be identified as a covariate on clearance in Japanese paediatric patients [93]. Lower serum AMB concentrations were also observed in children (17 days to 15 years old) receiving D-AMB [101], and body weight was found to be correlated with clearance and V_d [101, 102]. .

One study reported on Sb pharmacokinetics in children. In treating both adults and children with 20 mg Sb/kg daily, children reach only 58% of the AUC_{24} that adults reach [11]. Changing the dose in children to 30 mg/kg increased paediatric exposure to 86% of adult exposure after 20 mg/kg. As expected, children have a higher weight-adjusted clearance (0.185 L/h/kg) than adults (0.106 L/h/kg), indicating that elimination does not change in direct proportion to weight.

In a large-scale paromomycin phase III trial in India (313 adults and 188 children aged 5–14 years old), no significant differences were found in paromomycin pharmacokinetics between adults and children [33, 38]. The C_{max} of children (18.3 ± 8.26 μg/mL) was comparable to that of subjects older than 30 years (19.1 ± 9.75 μg/mL) [38]. However, the same study reported weight to be a significant covariate on V_d and clearance.

For pentamidine, concentration–time profiles were only available for two children (0.4 and 6 years old) and resembled the adult curves [57]. However, further investigation is required with a larger sample size to characterise pentamidine pharmacokinetics in paediatric patients.

4.2 HIV–Visceral Leishmaniasis Co-Infected Patients

In 2–9% of VL cases, patients are co-infected with HIV, but this percentage rises to 40% in specific patient populations (reviewed in Alvar et al. [103]). Co-infection of HIV with VL results in rapid disease progression, more severe disease and a poor treatment response. Treatment options are limited in HIV-positive VL patients due to higher toxicity levels, generally low cure rates, high relapse rates and higher fatality than in immunocompetent patients [103].

As antiretroviral and antileishmanial drugs are thus often administered concurrently, possible drug–drug interactions could take place and should be evaluated. The pharmacokinetics of antiretroviral drugs have been reviewed previously [104]. Protease inhibitors are known inhibitors of CYP2D6 (only ritonavir) and CYP3A (all protease inhibitors) and their combination with pentamidine should therefore be monitored, as pentamidine has in vitro been found to be metabolised by these CYP enzymes. In addition, most non-nucleoside reverse transcriptase inhibitors (NNRTIs), such as nevirapine and efavirenz, are CYP3A enzyme inducers and combination with pentamidine could lead to suboptimal pentamidine exposure [105]. As other antileishmanial drugs are not metabolised by CYP enzymes, interactions on this level are not expected. The pharmacokinetics of pentamidine have been studied in AIDS patients, but their specific antiretroviral treatment was not reported [53, 54, 57]. It should be mentioned that protease inhibitors were not available at that time.

Vice versa, selective inhibition of CYP450 enzymes was observed in rats treated with D-AMB, assumed to be due to an impairment of monooxygenases on the endoplasmic reticulum [106]. This inhibitory effect on CYP450 activity was confirmed in humans [107]. This could increase exposure to NNRTIs, protease inhibitors and entry inhibitors as they are extensively metabolised by CYP450 enzymes. L-AMB did not affect CYP activity in rats [106].

Due to the high prevalence of nephrotoxicity on D-AMB treatment, drug–drug interactions should be expected with mostly renally cleared nucleoside reverse transcriptase inhibitors (NRTIs) such as lamivudine and emtricitabine. Concomitant use with other possibly nephrotoxic antiretrovirals, such as tenofovir, must also be closely monitored for renal function. Drug–drug interactions have not been evaluated in L-AMB and are expected to be much less pronounced due to the decreased nephrotoxicity. Extra caution is also required when combining the renally cleared Sb and paromomycin with antiretroviral drugs causing nephrotoxicity, such as tenofovir, as this could possibly affect antileishmanial drug exposure. Furthermore, as both pentamidine and nevirapine can be hepatotoxic, combination of these drugs should be monitored.

Miltefosine has in vitro been revealed to inhibit intestinal P-glycoprotein (P-gp) with short-term exposure. This suggests potential drug–drug interactions with substrates of intestinal P-gp [108], such as all protease inhibitors and the NRTI tenofovir alafenamide. In addition, as miltefosine has been found to widen tight junctions and promotes its own paracellular transport, other oral (hydrophilic) compounds relying on paracellular transport such as lamivudine and zidovudine might also be increasingly absorbed, influencing oral bioavailability [108].

Furthermore, for the antiretroviral drugs with high protein binding to albumin, such as efavirenz and raltegravir, competition for protein binding could take place with the highly protein-bound antileishmanial drugs pentamidine (~70%), miltefosine (96–98%) and AMB (>90%). This could particularly be a problem in VL patients, who generally have severely lowered albumin levels [109, 110].

Pentamidine pharmacokinetics have been evaluated in AIDS patients but, due to the large heterogeneity of patients within studies and between studies, no conclusions can be drawn on potential differences with non-HIV patients. D-AMB pharmacokinetic parameters in five HIV patients [111] were in line with studies published for non-HIV patients (C_{max} 0.72 μg/mL after 0.3 mg/kg dosing and 9.48 mL/h/kg clearance). The pharmacokinetics of other antileishmanial drugs have not been evaluated in HIV patients or HIV co-infected VL patients.

In addition, antiretroviral drug pharmacokinetics have not been evaluated in VL patients. VL causes a disruption of liver physiology, potentially affecting exposure of co-infected patients to NNRTIs and protease inhibitors given their metabolism by liver (CYP) enzymes.

Therefore, it is necessary to study the pharmacokinetics of these drugs in this difficult-to-treat patient population. One study has recently been performed investigating L-AMB in monotherapy and in combination therapy with miltefosine in HIV-VL co-infected patients in Ethiopia also receiving antiretroviral treatment (NCT02011958 [139]), but results have not been published yet.

4.3 Pregnancy

Treatment options for pregnant women are particularly limited in leishmaniasis patients. The use of pentavalent antimonials, pentamidine and miltefosine is

contraindicated in pregnancy (FDA categories C, C and D, respectively), and thus the only treatment options are paromomycin (no category assigned) and AMB (FDA category B) (reviewed in Fontenele e Silva et al. [112]). The physiological changes in pregnant women are known to possibly alter the ADME of drugs and could thus potentially affect the exposure to drugs. Furthermore, long $t_{½}$ values of antileishmanial drugs might also require the use of contraceptives in women of reproductive age.

Sb has been correlated with adverse pregnancy outcomes (such as abortions, preterm births and stillbirths) [113–115]. Evidence for the mutagenic, carcinogenic and teratogenic effect of Sb is still scarce, but should probably be assumed [116]. Placental transfer of Sb was established in rats and Sb was transferred to pups via milk [117, 118]. At a daily dose of 300 mg Sb/kg, fetal growth retardation and increased embryo lethality and skeleton anomalies were observed [117, 119].

An obstacle to the widespread use of miltefosine in the clinic is its potential reproductive toxicity, reported as a result of pre-clinical in vivo studies in rats and rabbits [64]. Treatment of rats with miltefosine 1–2 mg/kg in early embryonic development and organogenesis resulted in embryotoxic, fetotoxic and teratogenic risk, indicating placental transfer [64]. While pentamidine in theory could hold teratogenic properties due to its inhibition of protein and nucleic acid synthesis in vitro, rat studies found a feticidal but not teratogenic effect in doses similar to human recommended dosages [120].

Both miltefosine and pentamidine have long terminal $t_{½}$ values. Miltefosine concentrations are still detectable in plasma up to 6 months after the end of treatment [70], and could thus still be harmful during pregnancy for long periods after end of treatment. A translational pharmacokinetic study advised that the duration of contraceptive use after treatment be 4 months after a 28-day miltefosine treatment, with a <0.1% probability of exceeding the NOAEL (no-observed-adverse-effect level) [121]. Pentamidine also has a relatively long terminal $t_{½}$ of ~12 days, which could have implications for the contraceptive duration required; however, this has not been studied.

Both paromomycin and AMB are not contraindicated in treatment of leishmaniasis patients. However, no studies have been performed on the pharmacokinetics of both antileishmanial drugs in pregnant or breastfeeding women. Animal studies (rat and rabbit) show that paromomycin is not teratogenic [32]. There are some worries about possible ototoxicity in the unborn child, as the aminoglycoside streptomycin has been reported to have possibly caused cases of ototoxicity in the unborn child when administered to women during pregnancy [122]. No studies have been performed on the excretion of paromomycin into breast milk; however, due to its poor lipid solubility and limited distribution, substantial excretion in breast milk is not expected. AMB has been found to cross the placenta in cord blood:maternal serum ratios between 0.38 and 1.51 (reviewed in Pilmis et al. [123]). Rodent and rabbit studies showed no teratogenicity at ten times the recommended human dose (reviewed in Pilmis et al. [123]).

4.4 Patients with Renal Impairment

The main route of elimination of both Sb and paromomycin is renal clearance, and they can thus be expected to be drastically impacted by renal impairment. Only a single report describes Sb pharmacokinetics in a VL patient with acute renal failure (glomerular filtration rate of 16 mL/min). After treatment with 25 mg MA/kg daily, C_{max} was elevated (22.9 µg/mL), C_{trough} was particularly high at 9.3 µg/mL and the $t_{½}$ was more than seven times higher (15 h) than in patients with normal renal function. The paromomycin $t_{½}$ was increased from 2.47 h for normal subjects to 6.7 h for patients with a creatinine clearance of 30–60 mL/min and was as high as 36.6 h for patients with a creatinine clearance of less than 10 mL/min [124]. In treating patients with renal impairment, Sb and paromomycin dose reductions are therefore advised.

For D-AMB, ~20% of the administered dose is renally excreted within 1 week. No pharmacokinetic parameters have been defined for patients with renal impairment, but a dose of D-AMB 1 mg/kg was well-tolerated in a VL patient on haemodialysis [125]. No AMB could be identified in peritoneal dialysate [126], as expected due to high AMB protein binding.

For pentamidine, miltefosine and L-AMB, no effect of renal impairment on pharmacokinetic parameters is expected, as only a small percentage is cleared by the kidneys (pentamidine/L-AMB <5% [53, 54, 57, 87], miltefosine <0.2% [61]). Pentamidine pharmacokinetic parameters were indeed not significantly different in patients with impaired renal function, receiving haemodialysis or peritoneal dialysis compared with patients with normal renal function [54, 57]. No results have been published on miltefosine pharmacokinetics in patients with renal impairment, but haemodialysis did not affect steady-state miltefosine concentrations in two patients with terminal renal failure (Kip and Dorlo, unpublished data). After L-AMB administration, the AMB concentration–time profiles were also not affected by haemodialysis or haemofiltration [95, 127], implying that AMB does not pass through extracorporal filtration membranes. In contrast, another study found a higher total AMB clearance in critically ill patients receiving continuous veno-venous hemofiltration (0.14 L/h/kg) than in patients

that do not (0.061 L/h/kg), though no significant differences in C_{max} and AUC_{24} were observed [128].

5 Drug–Drug Interactions Between Antileishmanial Drugs

In specific patient populations and certain regions, the antileishmanial drugs currently available are not sufficient due to lack of efficacy, increasing drug resistance, parenteral administration or severe adverse effects. Combining several antileishmanial drugs could possibly solve these issues and improve the therapeutic outcome in leishmaniasis treatment. In addition, it could shorten treatment duration. In the clinical studies on combination therapies performed to date, no clinical pharmacokinetic evaluations of drug–drug interactions have been performed, but pharmacokinetic interactions could potentially affect the safety of and exposure to the independent drugs.

Caution is required in the combination of D-AMB with paromomycin or pentamidine due to the possibility of cumulative risk of nephrotoxicity. In addition, the metabolism of pentamidine could potentially be affected due to CYP inhibition by D-AMB [106]. Furthermore, as both Sb and paromomycin are renally excreted, their combination with nephrotoxic antileishmanials (especially D-AMB) should be monitored.

As described previously, miltefosine was found to be an intestinal P-gp inhibitor and AMB was reported to be a substrate for P-gp [129], although this has been contested [130]. As both miltefosine and AMB are amphiphilic molecules, AMB monomers were found to be incorporated in micellar formations of miltefosine if miltefosine is present at levels above its critical micelle concentration [131]. This could alter the drug distribution of both AMB and miltefosine. Further information on the pharmacokinetics of combined administration of miltefosine and AMB will arise from a clinical study currently being conducted in Ethiopia (NCT02011958 [139]).

6 Directions for Future Advancements in Clinical Pharmacokinetic Research in Leishmaniasis

To date, clinical pharmacokinetic studies have only been performed in leishmaniasis patients for Sb, paromomycin and miltefosine. Performing these studies also for pentamidine and AMB is crucial in rationalising treatment design, as VL could potentially affect the pharmacokinetics of pentamidine and AMB due to alterations in hepatic physiology and clinical conditions such as hypoalbuminaemia.

For the drugs systemically administered in treatment of CL, limited information is available on the distribution of the drug towards the skin or skin lesions, which forms the target site of action. In addition, only one study evaluated intracellular drug concentrations. As the *Leishmania* parasite resides within macrophages, and most antileishmanial drugs exert their action intracellularly, future research should elaborate on intracellular drug exposure. Especially for Sb^{V}, which is converted into the active Sb^{III} intracellularly, these concentrations probably more accurately reflect the effective drug concentration to which the parasite is exposed. Information on the intracellular drug pharmacokinetics could be particularly useful to establish exposure–response relationships.

Furthermore, exposure–response studies linking the pharmacokinetics of antileishmanial drugs to treatment outcome have only been performed for miltefosine to date [72] (Dorlo et al., unpublished data). These studies are essential in the rationalisation of the dose, the schedule of antileishmanial treatment and the combination of different antileishmanial drugs. In addition, defining exposure–response relationships is especially important in investigating the possible pharmacokinetic basis for drug resistance.

More research is required in optimising dosing regimens for paediatric patients. Though efforts have been made to specifically evaluate different dosing regimens in paediatric leishmaniasis patients, special dosing regimens are currently only being clinically evaluated for miltefosine, while an adjusted dosage has also been proposed for L-AMB [92].

Population pharmacokinetic modelling could be a valuable tool in future pharmacokinetic research, especially in drugs with large variability in exposure, such as L-AMB. Population pharmacokinetic modelling also provides the opportunity to evaluate the allometric scaling of body size on clearance and V_d. Furthermore, full pharmacokinetic analysis can be performed with relatively limited sampling. Sparse sampling is particularly convenient in pharmacokinetic studies of antileishmanial drugs, as approximately half of the population is paediatric, requiring less intensive sampling schemes. Furthermore, clinical trials are often conducted in remote settings, making sampling and follow-up difficult, and consistent timing of sampling required for non-compartmental analysis is therefore challenging. For these sparse and heterogeneously collected pharmacokinetic samples, population pharmacokinetic modelling is especially valuable.

Regarding pharmacokinetic sampling, there is room for improvement by employing newer collection techniques such as the less invasive dried blood spot sampling [132]. Dried blood spot samples can be stored and shipped at room temperature, simplifying pharmacokinetic sampling, enabling easier sample transport logistics, and reducing costs, which is particularly valuable in remote and resource-poor VL and CL areas of endemicity.

Compliance with Ethical Standards

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