EXPERT REVIEWS

Pharmacokinetic variability of anthelmintics: implications for the treatment of neurocysticercosis

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Human neurocysticercosis is a severe disease caused by the installation of *Taenia solium* larvae in the CNS. A wide variety of clinical manifestations are related to neurocysticercosis. These are determined by a number of important factors, including the number and location of the cysts, the stage of cystercerci and the host response to the infection. Epilepsy, focal neurological signs and increased intracranial pressure are the most common clinical manifestations of the disease. Neurocysticercosis is still deeply rooted in Latin America, Africa and Asia. Albendazole and praziquantel are the drugs used in the treatment of cysticercosis. Both drugs have limited solubility and extensive metabolism, and thus great interindividual variability in plasma levels is found. This article focuses on current knowledge of the pharmacokinetics and the drug interactions of the anthelmintic drugs and the perspectives in the treatment of this parasitic disease.

Keywords: albendazole • bioavailability • drug interactions • neurocysticercosis • pharmacokinetics • praziquantel

Neurocysticercosis

Neurocysticercosis is the most common helminthic disease of the nervous system and still represents a serious threat to health in most Asian, African and Latin American countries [1,2]. Moreover, it is currently also considered an emergent disease in developed countries, due to the increase in migration [3,4]. Transmission-favoring conditions, related to poverty, that still exist in endemic countries and the absence of control campaigns have certainly contributed to the persistence of neurocysticercosis.

Cysticercosis results from the accidental ingestion of *Taenia solium* (pork tapeworm) eggs, usually from food contaminated by people with taeniasis. The life cycle of *T. solium* is shown in Figure 1. Once the eggs are in the GI tract, they are liberated from their coats by the actions of bile and pancreatic enzymes and become tiny larvae called oncospheres, which penetrate the intestinal wall and enter the bloodstream. Here, they are carried to muscles or other tissue of the host, including the brain, where the oncospheres transform into cysticerci and encyst. There, they can remain as viable cysts for years. The parasite life cycle is completed, resulting in human tapeworm infection, when humans ingest undercooked pork containing cysticerci [5].

Neurocysticercosis is clinically a pleomorphic disease that may be asymptomatic or manifest as a variety of nonspecific mild to severe neurologic syndromes. Clinical signs in neurocysticercosis depend on the number, size and stage of cysts, CNS location and the severity of the inflammatory response against the parasites. Common clinical manifestations include epilepsy, focal neurological signs, intracranial hypertension and cognitive decline [6].

Owing to the highly heterogeneous clinical presentations of neurocysticercosis, treatment should be individualized. Parasite number, localization, size and intensity of CNS inflammation must be taken into account before deciding upon the treatment [7]. Treatment of neurocysticercosis includes the following main therapeutic approaches: cysticidal drugs; corticosteroids for treatment of inflammation and/or surgical measures to control increased intracranial pressure; and other drugs for the treatment of neurological symptoms such as epilepsy, headache and behavioral disturbances [6].

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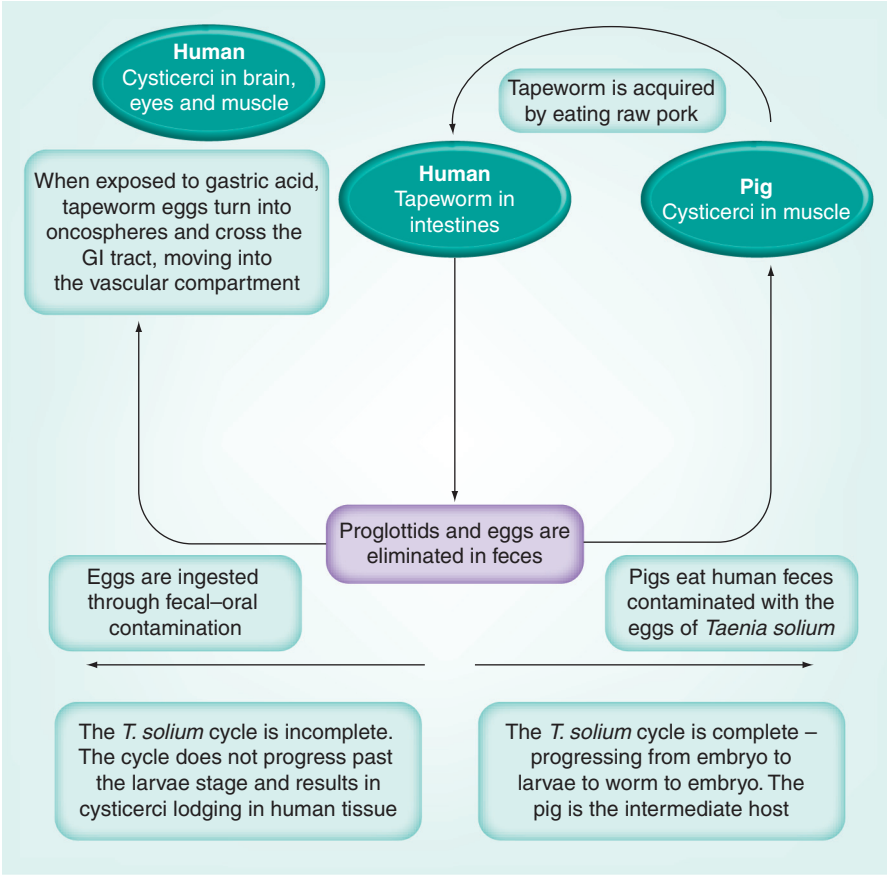

Figure 1. Life cycle of *Taenia solium*.

Current pharmacological treatment for neurocysticercosis comprises the use of praziquantel (PZQ) and albendazole (ABZ). PZQ has been available since 1979 and ABZ has been in use since 1987. The dose of PZQ used in most studies is 50 mg/kg/day in three divided doses over a period of 2 weeks. In the case of ABZ, the current dosage regimen for the treatment of the disease is 15 mg/kg/day every 8 h over a period of 8 days. Treatment with a dose of 30 mg/kg/day every 8 h for 8 days for subarachnoid and intraventricular cysticercosis has also been used. Although both drugs are proven cysticidal agents, their effectiveness is variable. While some patients require one course, others require repeated courses, and in some cases treatment failure has been reported. Parasite localization is one of the main factors involved in the success of the therapy. When the parasites are located in the parenchyma, the use of cysticidal drug therapy has shown an increased resolution of lesions on imaging and clinical improvement in most of the patients; however, in some cases, only a modest effect is reported [8,9]. When the parasites are located in the subarachnoid basal cisterns, the prognosis is more uncertain [10–13]. The precise causes of the parasite's persistence are still unknown; multiple host and parasite factors may be involved.

Praziquantel

PZQ is a broad-spectrum antihelmintic agent with strong action against schistosomes and cestodes. The drug was first developed for the veterinary market and then for the human market. Its curative efficacy against various helminths pathogenic to man was confirmed during the 1970s. The compound was patented in Germany in December 1973 and in the USA in 1977. PZQ became available on the international market in the 1980s [14]. The drug has been used for human cysticercosis treatment since a beneficial response was documented [15].

The exact mechanism of action of PZQ remains uncertain. PZQ affects the motility of the parasite characterized by rapid and sustained muscular contraction followed by tegumental disruption that leads to exposure of parasite antigens on the surface. These effects are attributed to the interaction of PZQ with specific Ca^{2+} sites in the tegument and muscle cells of the parasite [16].

PZQ is a chiral drug available as a racemic mixture. The oral route is the only approved route for PZQ administration in humans. The drug is a highly lipophilic and is well absorbed from the GI tract. The absolute bioavailability has not been determined in humans; however, it has been shown that the drug is extensively metabolized to mono-, di- and tri-hydroxylated compounds by cytochrome P450 (CYP)1A2, CYP3A4 and CYP2C19 in human liver microsomes. Two main metabolites have been fully identified and described, as *cis*-4-hydroxypraziquantel and *trans*-4-hydroxypraziquantel (4-OHPZQ). It has been shown that in humans, the 4-OHPZQ metabolite is far more abundant [17]. In a clinical study, enantioselectivity in the kinetic disposition of PZQ and 4-OHPZQ was observed, showing a higher proportion of the (+)-(*S*)-PZQ and (-)-(*R*)-4-OHPZQ enantiomers in the plasma [18].

Studies regarding PZQ distribution are scarce. It has been found that the drug is 80–85% bound to plasma proteins. The drug permeates the blood–brain barrier, explaining its effectiveness on parenchymal brain cysticercosis. Concentrations in the breast milk reach approximately 25% of plasma concentration [7].

Overall clearance is rapid, with a half-life of 1–2 h [7]. In addition, it has been found that the pharmacokinetics of PZQ appear to be dose dependent, with the area under the curve (AUC) increasing by more than 20-fold (167 ± 51 to 3931 ± 1432 ng/ml) for a tenfold increase in dose [19]. No differences were detected between healthy subjects and patients with liver disease [20].

Table 1 shows the pharmacokinetic parameters of PZQ extracted from different studies in the adult population. In all the studies, the pharmacokinetic parameters were determined using a model-independent method. Most studies were performed in healthy volunteers. When PZQ was administered in fasting state, half-life values ranged between 1 and 3 h. In all the studies, a wide interindividual

Table 1. Mean pharmacokinetic parameters of praziquantel extracted from different studies in the adult population.

Study (year)	Population	Condition	C_{max} (ng/ml)	AUC (ng.h/ml)	T_{max} (h)	$T_{1/2}$ (h)	Dose	Ref.
Castro *et al.* (2000) NC	HV (n = 9), crossover	Fasting state High-fat diet High-carbohydrate diet	318.8 (227) 1095 (780) 1962 (780)	882 (417) 2474 (1166) 3276 (969)	1.39 (0.98) 1.94 (1.1) 1.47 (0.64)	2.03 (0.24) 1.72 (1.1) 1.66 (0.64)	1800 mg 1800 mg 1800 mg	[27]
Metwally *et al.* (1995) NC	HV (n = 10) HV (n = 10)	Biltricid	0.846 (0.211) 2.18 (0.29)	1303 (276) 3550 (883)	1.65 (2.11) 2.0 (1.65)	0.97 (0.186) 1.28 (0.371)	20 mg/kg 40 mg/kg	[48]
Watt *et al.* (1988) NC	No liver disease (n = 13) Moderate liver disease (n = 9) Severe liver disease (n = 8)	PZQ Patients with schistosomiasis	2.17 (1.14) 5.01 (2.47) 8.195 (4.86)	8940 (4250) 22888 (1582) 37770 (2450)	2.5 (1.7) 1.9 (1.3) 2.6 (2.0)	1.7 (0.8) 2.2 (0.6) 2.3 (1.0)	60 mg/kg 60 mg/kg 60 mg/kg	[20]
Castro *et al.* (2002) NC	HV (n = 9), crossover	Fasting state Grapefruit juice	637.7 (128.3) 1037.6 (305.37)	1387 (240.5) 2639 (786.9)	1.77 (0.24) 2.1 (0.16)	1.8 (0.17) 1.7 (0.11)	1800 mg 1800 mg	[24]
Jung *et al.* (1997) NC	HV (n = 8), crossover	Fasting state Cimetidine		7410 (2780) 14210 (4590)		1.8 (0.4) 2.2 (0.3)	Three oral doses 25 mg/kg at 2 h intervals	[23]
Ridtitid *et al.* (2007) NC	HV (n = 10), crossover	PZQ alone	183.38 (43.90)	955.94 (307.74)	2.05 (0.36)	3.8 (0.96)	PZQ 20 mg/kg	[21]
		PZQ + ketoconazole	371.31 (44.63)	1843.10 (336.39)	1.83 (0.3)	4.05 (0.76)	PZQ 20 mg/kg + ketoconazole (400 mg/5 days)	
Ridtitid *et al.* (2002) NC	HV (n = 10), crossover	PZQ alone	740 (210)	4240 (435)	2.7 (1.5)	2.9 (1.5)	PZQ 40 mg/kg	[26]
		PZQ + rifampin	143 (50)	630 (348)	2.3 (1.5)	2.3 (1.6)	PZQ 40 mg/kg + 600 mg/5 days (rifampin)	
	HV (n = 10), crossover	PZQ multiple dose alone	734 (377)	3018 (1067)	1.9 (1.2)	3.2 (0.8)	PZQ 25 mg/kg (3 doses)	
		PZQ multiple dose + rifampin	194 (43)	602 (151)	2.2 (1.4)	1.9 (0.3)	PZQ 25 mg/kg + 600 mg/5 days (rifampin)	

Standard deviations are written in round brackets and ranges are given in square brackets.
ABZ: Albendazole; AUC: Area under the curve; HV: Healthy volunteer; MCM: Monocompartmental model; NC: Noncompartmental analysis; PZQ: Praziquantel; $T_{1/2}$: Half-life; T_{max}: Time to peak plasma concentration.

Table 1. Mean pharmacokinetic parameters of praziquantel extracted from different studies in the adult population (cont.).

Study (year)	Population	Condition	C_{max} (ng/ml)	AUC (ng·h/ml)	T_{max} (h)	$T_{1/2}$ (h)	Dose	Ref.
Na-Bangchang *et al.* (2006) NC	HV (n = 23), three-way crossover	PZQ alone	784 (381)	3282 (1732)	2.0 (0.9)	1.7 [8–3.1]	40 mg/kg PZQ	[22]
		PZQ + ABZ + ivermectin	765 (351)	3308 (1705)	2.1 (0.9	1.6 [6–2.8]	20 µg/kg ivermectin + 400 mg ABZ + 40 mg/kg PZQ	
Lima *et al.* (2010) MCM	HV (n = 9), crossover study (3 × 3)	**PZQ**						[41]
		(+)-(*S*)-PZQ	520 [960–5020]	2990 [610–1970]	2.55 [2.14–2.95]	1.46 [1.21– 1.71]	1500 mg	
		(-)(*R*)–PZQ	870 [90–1640]	170 [70–250]	2.67 [2.15–3.19]	1.55 [1.24–1.85]		
		PZQ + ABZ						
		(+)-(*S*)-PZQ	450 [240–660]	3030 [450–4610]	2.76 [2.26–3.26]	12.87 [9.58–16.17]	1500 mg + 400 mg	
		(-)(*R*)-PZQ	240 [70–420]	1530 [220–2840]	2.73 [2.13–3.32]	4.09 [2.28–5.91]		

Standard deviations are written in round brackets and ranges are given in square brackets.
ABZ: Albendazole; AUC: Area under the curve; HV: Healthy volunteer; MCM: Monocompartmental model; NC: Noncompartmental analysis; PZQ: Praziquantel; $T_{1/2}$: Half-life; T_{max}: Time to peak plasma concentration.

variability in C_{max} and AUC was found. Coefficients of variation were close to 50% for both parameters. In addition, mean total clearance (CL/F) values show great interindividual variability: 2.65 ± 0.64 ml/h/kg and 3.31 ml/h/kg (1.48–18.18 ml/h/kg) [21,22]. Possible reasons for this variability include the limited aqueous solubility of the drug (leading to variable bioavailability), variable hepatic metabolism, race or gender. Metabolism is the most crucial and complex step of drug disposition and could be the major source of pharmacokinetic variability.

PZQ interactions

Interactions between PZQ and other concomitantly given drugs is another aspect that could contribute to the variability in pharmacokinetic parameters. It has been shown that administration of PZQ with CYP3A4 inhibitors, such as cimetidine [23], ketoconazole or grapefruit juice, markedly increased the plasma levels and AUC of PZQ. In the case of ketoconazole, the mean AUC and C_{max} of PZQ increased by 93 and 102%, respectively, whereas the CL/F of PZQ was significantly decreased by 58% [21]. Concomitant administration with grapefruit juice increased AUC by 1.9-fold [24]. Considering that in most of these studies the rate of elimination was not modified, the data suggest that the liver intrinsic capacity to eliminate PZQ from the systemic circulation is less affected.

Early studies reported that potent CYP3A4 inducers decreased the plasma concentration of PZQ as a result of increased clearance due to induction of first-pass hepatic metabolism. Thus, the antiepileptic drugs carbamazepine and phenytoin substantially reduce the PZQ bioavailability. AUC and C_{max} were reduced by 90.3 and 92.1%, respectively, in carbamazepine-treated subjects when compared with control subjects, while AUC and C_{max} were reduced by 74 and 76%, respectively, in phenytoin-treated subjects when compared with control subjects [25]. Simultaneous administration of PZQ and dexamethasone reduces peak plasma levels as well as steady-state levels, by approximately 50% [7]. In addition, rifampin greatly decreased C_{max} and AUC of single and multiple oral doses of PZQ [26]. In the single-dose study, C_{max} and AUC were reduced by approximately 99 and 94%, respectively, and in the multiple-dose study they were reduced by 98 and 89%, respectively [26]. These interactions could contribute to the therapeutic failure of PZQ.

With regard to concomitant medication or diet, food significantly enhances PZQ absorption in man. The relative bioavailability of PZQ was increased by a factor of 2.72 and 3.98 when the drug was administered with a high-lipid and high-carbohydrate diet, respectively, which could be related to tablet disintegration, better drug dissolution or other factors, such as changes in hepatic blood flow or in the metabolism of the drug during the first passage through the liver [27].

Considering that patients with neurocysticercosis commonly require multiple drug therapy, careful evaluation of the potential drug interactions should be performed in order to assure drug efficacy. A population pharmacokinetic study could help to identify the demographic, pathophysiological, environmental and drug-related patient factors that contribute to the variability observed with this drug.

Albendazole

ABZ is a broad-spectrum synthetic antiparasitic agent, which is active against intestinal roundworms, lungworms and tapeworms. The study of ABZ for human medicine was initiated in 1979. In 1983, it was used for hydatidosis treatment [7]. In 1987, Escobedo *et al.* showed that the drug was effective in the treatment of neurocysticercosis [28], and today it is considered the drug of choice for to treat this disease, because of slightly greater cure rates, apparent increased efficacy in subarachnoid or ventricular cysts, and reduced cost [8].

It has been found that ABZ causes degenerative alterations in the tegument cells of the parasite by binding to the colchicine-sensitive site of tubulin, thus inhibiting its polymerization or assembly into microtubules. This causes the disruption of the parasite metabolism, including decrease of glucose uptake and cholinesterase secretion, which leads to immobilization and eventual parasite death. A secondary action of ABZ may be the inhibition of the enzyme fumarate reductase, which is helminth specific [29].

ABZ is a poorly soluble drug in water and, consequently, it is poorly absorbed from the GI tract and its oral bioavailability is low. The drug undergoes extensive and rapid first-pass metabolism by flavin mono-oxygenases and by the CYP system (mainly CYP3A4) into the chiral metabolite ABZ sulfoxide [(+)-ASOX; (-)-ASOX)], which possesses anthelmintic activity, and into the non-chiral metabolite ABZ sulfone (ASON), which lacks pharmacological activity. The kinetic disposition of ASOX is enantioselective, with (+)/(-) ratios of area under the plasma concentration–time curve of approximately 10 in patients with neurocysticercosis treated with ABZ [30]. Enantiomer (-)ASOX is dominant in rats and mice, while (+)ASOX is dominant in sheep, goats, dogs, cattle and humans. Plasma concentrations of the metabolites ASOX and ASON are higher than those of the parent drug. Although ASOX is considered to be the active metabolite, ABZ also has cysticidal activity [31].

ABZ is highly bound to plasma proteins (89–92%), while AZOX is bound to a lesser extent (62–77%). ASOX is also found in the brain and a high proportion of the drug reaches the cerebrospinal fluid (CSF) compared with its concentration in plasma (2:1 plasma to CSF ratio) [7]. ASOX permeates the blood–brain barrier. This fact explains the efficacy of ABZ in the treatment of parenchymal cysticercosis. It has been shown that the ASOX concentration in CSF displays high interindividual variability, which could be related to the variability in the pharmacokinetics of the drug. Other factors such as age, gender and inflammation of the subarachnoid space were not related to this variability [7].

ASOX has also been detected in milk samples of lactating women until 36 h after administration of a single oral dose of ABZ. The ratio of milk–serum concentration at 6 h was 0.6 (0.1–1.5) [32]. Additionally, the breast cancer resistance protein BCRP/ABCG2 is involved in the transport of ASOX into breast milk [33].

The first evidence of the high variability of ABZ pharmacokinetics was published in 1986 by Marriner *et al.* [34]. In this study, the maximum concentration of ASOX varied from 0.04 to 0.55 µg/ml. Furthermore, AUC values ranged from 0.42 to 8.95 µg·h/ml. The wide differences were attributed to differences in absorption rather than differences in metabolism.

Table 2 shows the pharmacokinetic parameters of ABZ sulfoxide extracted from different studies, which were performed in healthy volunteers or patients. A study in lactating women is also included. It can be observed that mean half-life values in healthy volunteers ranged between 8 and 10 h; however, in patients, the mean values were lower (4–7 h). Further studies are required to explain these differences. The CL/F values for ASOX have not recently been reported.

As seen in Table 2, different doses and drug combinations have been evaluated; however, interindividual variability is common. This variability has been also observed in CSF. After a dose of 50 mg/kg, ASOX concentrations in CSF ranged between 0.063 and 1.2 µg/ml [35]. These unpredictable concentrations probably explain failure of cure in some patients; nevertheless, it has not been proven.

In order to explain the variability, a population pharmacokinetic analysis in 90 patients with neurocysticercosis receiving 30 mg/kg/day of ABZ was recently performed [36]. The population analysis was performed using non-linear, mixed-effect modeling. A one compartmental model with first order absorption and elimination was used. Results showed that other than bodyweight, the readily available covariates as age, sex, creatinine clearance or patient status (hospitalized vs ambulatory) do not substantially account for the large patient variability. The variability found in ASOX pharmacokinetics and plasma levels could probably be due to problems related to its bioavailability, considering that a quarter of the population absorbed as little as 30% of the drug relative to the others. These low drug absorptions might be responsible for treatment failures.

Albendazole interactions

In neurocysticercosis, ABZ is administered with food or concomitant medications including steroids, H_2 blockers and antiepileptic drugs, which can affect the pharmacokinetics of the drug. When combined with a fatty meal, maximum ASOX concentration (C_{max}) in plasma increased by 4.5–9-fold [37]. Apparently, the presence of neutral fat in the duodenum may increase bile flow and improve the absorption of ABZ by the detergent action of the bile acids. The mechanism remains to be demonstrated.

When ABZ is administered with phenytoin, carbamazepine or phenobarbital, a significant reduction in the plasma concentration of ASOX metabolite has been found [38]. When ABZ was coadministered with cimetidine, a 52% decrease in ASOX C_{max} values was seen (probably due to inhibition of gastric acid secretion), suggesting that absorption is pH dependent. When coadministered with grapefruit juice, the ASOX C_{max} was enhanced by 3.2-fold, probably due to inhibition of the intraluminal degradation of ABZ by CYP3A4 enzymes [39]. Half-life and AUC of ASOX increased by average of 54 and 105% when dexamethasone was given simultaneously [40].

Lima *et al.* evaluated the pharmacokinetic interaction between ABZ and PZQ in healthy volunteers [41]. The results showed that the interaction is enantioselective. Thus, PZQ increased the AUC of (+)-ASOX by 264% (0.99 vs 2.59 $\mu g \cdot ml^{-1}$ h), (-)-ASOX by 358% (0.14 vs 0.50 $\mu g \cdot ml^{-1}$ h) and ASON by 187% (0.17

Table 2. Mean pharmacokinetic parameters of albendazole sulfoxide extracted from different studies in adult populations.

Study (year)	Population	Condition	C_{max} (ng/ml)	AUC (ng.h/ml)	T_{max} (h)	$T_{1/2}$ (h)	Dose	Ref.
Rigter *et al.* (2004) TCM	HV (n = 10), crossover	Tablet	300 (140)	4200 (1850)	3.18 (0.96)		800 mg	[49]
		Suspension (arachis oil/ polysorbate 80)	1430 (47)	18220 (8530)	3.37 (1.62)		800 mg	
		Cyclodextrin solution	2770 (860)	40560 (23150)	4.36 (0.80)		800 mg	
Góngora-Rivera *et al.* (2006) NC	Patients with NCC (n = 14)	Steady-state plasma levels	1080 (700)				15 mg/kg/day for 8 days	[10]
		Steady-state CSF levels	510 (320)					
	Patients with NCC (n = 17)	Steady-state plasma levels	1480 (800)				30mg/kg/day for 8 days	
		Steady-state CSF levels	1360 (850)					
Mares *et al.* (2005) NC	HV (n = 16), crossover	Fasting state	250 (110)	5062 (277)	3.1 (1.1)	9.8 (3.9)	800 mg	[37]
		Fatty meal	1770 (160)	29356 (1453)	5.12 (1.58)	9.1 (2.01)	800 mg	
Nagy *et al.* (2002) NC	HV (n = 6)	Fasting state	240 (90)	2080 (610)	2.5 [1–4]	8.8 (4.2)	10 mg/kg	[39]
		Fatty meal	1550 (300)	19640 (681)	5.3 [3–8]	8.2 (4.3)	10 mg/kg	
		Grapefruit juice	760 (370)	6520 (509)	5.3 [4–6]	4.1 (1.6)	10 mg/kg	
		Grapefruit juice + cimetidine	410 (290)	3520 (185)	5.2 [4–6]	6.1 (1.9)	10 mg/kg	
Na-Bangchang *et al.* (2006) NC	HV (n = 23), crossover	Ivermectin + ABZ	245 [119–571]	2998 [1222–7005]	2.0 [2–3]	8.4 [4.6–11.5]	20 µg/kg ivermectin + 400 mg ABZ	[22]
		PZQ + ABZ + ivermectin	262 [148–688]	3943 [1905–7696]	2.0 [2–3]	8.1 [5.5–12]	20 µg/kg ivermectin + 400 mg ABZ + 40 mg/kg PZQ	
García *et al.* (2011) MCM	Patients with NC (n = 28)	**ABZ + placebo**						[42]
		First dose	100.5 [†]76.6–124.3	1111 [†]931.1–1290.8	3.6 [†]2.9–4.4	4.4 [†]3.1–5.8	15 mg/kg	
		Multiple dose	426.6 [†]352.1–501.2	2969.6 [†]2543.8 –3395	1.3 [†]1.1–1.6	6.1 [†]4.7–7.6	15 mg/kg (10 days)	
	(n = 30)	**ABZ + PZQ**						
		First dose	113.4 [†]80.3–146.5	1412.2 [†]1115.5 –1709	3.7 [†]2.6 -4.8	6.0 [†]4.2–7.7	15 mg/kg + 50 mg/kg	
		Multiple dose	608.7 [†]476.2–741.2	4925.3 [†]3548.6–6302	1.6 [†]0.9–2.4	6.3 [†]5.6–7.1	15 mg/kg + 50 mg/kg (10 days)	
Lima *et al.* (2010) MCM	HV (n = 9), crossover study (3 × 3)	**ABZ**						[41]
		(+) ASOX	48.64 [19.7–77.5]	1290 [610–1970]	3.72 [2.66–4.7]	17.31 [19.49–21.13]	400 mg	
		(-) ASOX	28.06 [8.02–48.1]	170 [70–250]	1.93 [0.88–2.99]	3.66 [19.7–77.5]		
		ABZ + PZQ						
		(+) ASOX	94.75 [41.9–147.51]	2220 [1110 –3332]	5.04 [3.4–6.67]	12.87 [9.58–16–7]	400 mg + 1500 mg	
		(-) ASOX	46.17 [24.4–67.91]	440 [200 –670]	2.67 [1.82–3.51]	4.09 [2.28–5.91]		

Standard deviations are written in round brackets, and ranges are given in square brackets.
[†]Denotes 95% CI.
[‡]Standardized breakfast consisted of 12 ounces of skim milk and one cereal (nutritional make-up: 235.65 kcal, 2.09 g fat, 3 g fiber, 15.68 g protein, 40.43 g carbohydrate, 551.5 mg calcium, 8.25 mg iron and 5.22 mg zinc).
ABZ: Albendazole; ASOX: Albendazole sulfoxide; AUC: Area under the curve; HV: Healthy volunteer; im.: Intramuscular; MCM: Monocompartmental model; NC: Non-compartmental analysis; NCC: Neurocysticercosis; $T_{1/2}$: Half-life; TCM: Two-compartment model; t.i.d.: Three-times daily; T_{max}: Time to peak plasma concentration.

Table 2. Mean pharmacokinetic parameters of albendazole sulfoxide extracted from different studies in adult populations (cont.).

Study (year)	Population	Condition	C_{max} (ng/ml)	AUC (ng.h/ml)	T_{max} (h)	$T_{1/2}$ (h)	Dose	Ref.
Takayanaguiet *al.* (1997) MCM	Patients with NCC (n = 8)	ABZ alone	510	2290	2.65	3.25	5 mg/kg t.i.d.	[40]
	(n = 8)	ABZ + dexamethasone	770	4700	3.0	5.0	5 mg/kg t.i.d. + dexamethasone im. 6 mg once a day	
	(n = 8)	ABZ + dexamethasone and cimetidine	1030	5870	2.65	5.2	5 mg/kg t.i.d. + dexamethasone im. 6 mg once a day + 800 mg cimetidine	
Amsden *et al.* (2007) NC	HV Three-way crossover (n = 18) Under standardized breakfast‡	Ivermectin + albendazole	495.6. (218.2)	6070 (3385)	3.54 (1.2)	19.4 (13.5)	Ivermectin (200 µg/kg) + 400 mg ABZ	[43]
		Azithromycin + ivermectin + ABZ	426.9 (182.1)	7547 (4737)	2.56 (0.82)	20.3 (16.6)	500 mg azythromicin + 400 mg ABZ + 200 µg/kg ivermectin	
		Azithromycin alone					500 mg	
Abdel-Tawab *et al.* (2009) NC	Lactating women (n = 33)	Breast milk levels	350 (32.4)	3932 (455)	12.4 (2.2)	6.9 (0.5)	400 mg	[32]

Standard deviations are written in round brackets, and ranges are given in square brackets.
†Denotes 95% CI.
‡Standardized breakfast consisted of 12 ounces of skim milk and one cereal (nutritional make-up: 235.65 kcal, 2.09 g fat, 3 g fiber, 15.68 g protein, 40.43 g carbohydrate, 551.5 mg calcium, 8.25 mg iron and 5.22 mg zinc).
ABZ: Albendazole; ASOX: Albendazole sulfoxide; AUC: Area under the curve; HV: Healthy volunteer; im.: Intramuscular; MCM: Monocompartmental model; NC: Non-compartmental analysis; NCC: Neurocysticercosis; $T_{1/2}$: Half-life; TCM: Two-compartment model; t.i.d.: Three-times daily; T_{max}: Time to peak plasma concentration.

vs 0.32 µg·ml^{-1} h). The administration of ABZ did not change the kinetic disposition of (+)-(*S*)-PZQ, (-)-(*R*)-4-OHPZQ or (+)-(*S*)-4-OHPZQ, but increased the AUC of (-)-(*R*)-PZQ by 64.77% (0.52 vs 0.86 µg·ml^{-1}h). The interaction was also evaluated in patients with neurocysticercosis. The results demonstrated that ASOX levels were increased in the combination group compared with the ABZ-alone group, both in patients taking phenytoin and patients taking carbamazepine. PZQ levels were also increased at the end of therapy. These increased levels could independently contribute to increase the cysticidal efficacy by itself or in addition to a possible synergistic effect [42].

Na-Bangchang *et al.* evaluated the pharmacokinetic interaction of ABZ, PZQ and ivermectin combinations in healthy volunteers [22]. Data showed that C_{max} and $AUC_{0-\infty}$ of ASOX were significantly higher (8 and 31%, respectively) following a regimen of ABZ + PZQ + ivermectin compared with an ABZ + ivermectin regimen; however, based on US FDA criteria, these changes were not considered to be of clinical relevance

Amsden *et al.* performed a pharmacokinetic study in order to evaluate the pharmacokinetic interaction of azithromycin with the combination of ivermectin and ABZ [43]. The results showed no interaction between azithromycin and ABZ, while the AUC of ivermectin increased in 31% after the combination. The increase of the exposure requires further investigation.

Approaches to increase the bioavailability of cysticidal drugs

Improvement of oral bioavailability is of clinical importance in the treatment of systemic helminthiasis. In order to enhance ABZ water solubility and its bioavailability, different strategies have been developed, such as the use of cyclodextrins, ternary complexes and nanoparticulated oral formulations. Thus, hydroxypropyl (HP) β-cyclodextrin increased the bioavailability and consequently the effectiveness of ABZ against encapsulated *Trichinella* larvae [44]. Kalaiselvan *et al.* explored the influence of carboxylic acids on the combination of ABZ with β-cyclodextrin and HP β-cyclodextrin [45]. Results showed that the ternary ABZ-HP β-cyclodextrin–tartaric acid complex improved the inclusion efficiency, solubility and dissolution in comparison to the binary

system. Furthermore, the bioavailability and anthelmintic efficacy of the drug complex against *Trichinella spiralis* was enhanced when compared with a commercial suspension. Recently, a different nanoparticulate oral formulation of ABZ was evaluated in rats showing that T_{max} was significantly reduced, C_{max} showed a twofold enhancement and bioavailability was increased by two-to-threefold compared with that of the market product. The increase in absorption rate of the formulation was attributed to the increase in surface area of the drug nanoparticles as well as the increase in solubility of the drug [46]. Further studies will be needed in order to determine the *in vivo* bioavailability as well as the efficacy of this formulation. In the case of PZQ, although many techniques have been employed to improve the oral bioavailability, most of them are used to improve its dissolution but it is not enough to improve its bioavailability as long as the released PZQ cannot bypass the liver first-pass effect. Yang *et al.* evaluated the feasibility of solid lipid nanoparticles to enhance its oral bioavailability [47]. They found that the mean residence time of PZQ was significantly increased when compared with the conventional tablet. The data indicate that solid lipid nanoparticles could be a promising drug carrier for PZQ; however, data in humans are not yet available.

Treatment of neurocysticercosis remains a difficult clinical problem. In the last 5 years, the information about the medical treatment of neurocysticercosis has increased considerably; however, little information is available regarding plasma level monitoring of ABZSX or PZQ. Doses administered are soley based on bodyweight, regardless of the concomitant medication. Taking into account the high interindividual variability and the potential drug interactions, large-scale studies should be performed in order to find a correlation between drug plasma levels and patient outcomes and then validate these findings in large clinical trials.

Expert commentary

Neurocysticercosis is still a public health problem in developing countries. Since the advent of ABZ and PZQ, no new drugs have been developed for the treatment of this disease. Both drugs show great interindividual variability in the pharmacokinetic parameters, which is also related to variability in plasma levels. ABZ variability has been attributed to its low bioavailability, while PZQ variability is related to its extensive metabolism. Antiepileptic drugs, as well as inducers and inhibitors of CYP3A4, also contribute to the variability. In order to improve the antihelmintic treatment in patients with neurocysticercosis, further investigation of the use of the population pharmacokinetic model is also recommended.

Five-year view

In the next 5 years, new therapeutic strategies for the treatment of neurocysticercosis will be developed. One such approach could be the development of new ABZ and PZQ formulations, with the aim of improving the bioavailability and therapeutic efficacy of the drugs. Another alternative might be the search for other pharmacological alternatives, such as oxfendazole, which has been shown to be useful in the treatment of cysticercosis in swine, or ivermectin, which seems to destroy cysticerci in patients resistant to cysticercidal drugs. Combinations of drugs with different mechanisms of action will be also be evaluated.

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Key issues

- Neurocysticercosis still represents a serious health threat in most Asian, African and Latin American countries.
- Albendazole (ABZ) and praziquantel (PZQ) are still the antiparasitic drugs of choice for the treatment of neurocysticercosis.
- The effectiveness of both drugs is variable.
- Metabolism is the most crucial and complex step of drug disposition for PZQ and can be a major source of pharmacokinetic variability.
- The variability reported in ABZ sulfoxide pharmacokinetics is probably due to differences in ABZ absorption and bioavailability.
- Plasma levels of ABZ and PZQ are affected by inhibitors and inducers.
- The combination of ABZ plus PZQ is associated with an increase in ABZ sulfoxide plasma concentrations and could be a potential alternative for treatment of neurocysticercosis.
- Therapeutic drug monitoring could be useful for those patients who do not respond to treatment.

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