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Abstract:

Neurocysticercosis (NC) or infection of the central nervous system with Taenia solium larvae is the leading cause of preventable epilepsy in endemic regions across the globe. Albendazole and praziquantel are commonly used antihelminthic agents to treat NC; however, viable cysts persist in the majority of patients, putting them at risk for future seizures and other neurological complications.

Because of their pharmacokinetic profiles, albendazole and praziquantel have the potential to interact with many different drugs. During antihelminthic treatment, antiepileptic drugs and corticosteroids are commonly co-administered to manage seizures and cerebral edema; however, the most commonly used agents from these drug classes are known to significantly alter plasma concentrations of albendazole and praziquantel.

The overarching issue with drug interactions during the treatment of NC is whether or not they have clinical relevance, as the plasma concentrations of albendazole and praziquantel have not been directly linked with eradication of viable cysts. Future studies should attempt to evaluate the validity of a causal relationship between antihelminthic plasma concentrations and outcomes so that drug interactions can be better understood and managed and so that treatment can be optimized.

Routine Drug and Food Interactions During Antihelminthic Treatment of Neurocysticercosis: a Reason for the Variable Efficacy of Albendazole and Praziquantel?

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Abstract

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Because of their pharmacokinetic profiles, albendazole and praziquantel have the potential to interact with many different drugs. During antihelminthic treatment, antiepileptic drugs and corticosteroids are commonly co-administered to manage seizures and cerebral edema; however, the most commonly used agents from these drug classes are known to significantly alter plasma concentrations of albendazole and praziquantel.

The overarching issue with drug interactions during the treatment of NC is whether or not they have clinical relevance, as the plasma concentrations of albendazole and praziquantel have not been directly linked with eradication of viable cysts. Future studies should attempt to evaluate the validity of a causal relationship between antihelminthic plasma concentrations and outcomes so that drug interactions can be better understood and managed and so that treatment can be optimized.

Introduction

Neurocysticercosis (NC), or central nervous system infection with the larval form of the cestode tapeworm *Taenia solium,* is the leading cause of preventable epilepsy in endemic regions of Africa, Asia, and Latin America.[1] In addition, cases of NC are increasingly seen in the United States and the European Union, as both have high immigration rates from endemic regions.[2,3] NC develops when *T. solium* eggs are ingested through the fecal-oral route (i.e., autoinfection or person-to-person transmission), cross the digestive tract into the blood stream and encyst in the central nervous system where they evolve through 4 stages.[4,5] After encysting, the vesicular stage begins, where the larva remains alive, protected by the cyst.[4] With natural evolution, the colloidal stage follows, where the cyst begins to degenerate, which is followed by the granular-nodular stage, where the wall of the cyst beings to thicken, and finally the calcified stage.[4] Cysts are only viable during the vesicular and colloidal stages, which are the only stages that respond to antihelminthic treatment.[4] NC may affect the brain parenchyma or infiltrate the cerebrospinal fluid primarily of the subarachnoid spaces and ventricles (i.e., extraparenchymal NC). The parenchymal location generally has a good prognosis; however, in contrast, the extraparenchymal location is associated with high morbidity and mortality.[5]

Antihelminthic treatment appears to have a role in reducing the number of viable cysts and potentially reducing the risk of seizures in patients with parenchymal NC.[4] It has been argued that the most important issue in the efficacy of NC treatment is the complete disappearance of cysts, as viable cysts eventually evolve into calcifications, which are

associated with increased risk for recurrent seizures and are not treatable with antihelminthic agents.[6] Two antihelminthic agents, albendazole and praziquantel, are used in clinical practice for the treatment of NC. Recent evidence-based guidelines found insufficient evidence to assess the efficacy of praziquantel, but currently recommend albendazole for the treatment of NC in both adults and children.[4] Of interest is that the dose and duration of antihelminthic regimens, even those tested in clinical trials, are empiric and have not been optimized through evidence-based research. Despite the availability of these two agents, cure rates remain suboptimal. In large clinical trials, treatment with albendazole only led to disappearance of viable cysts in about one-third of patients, after a first course of therapy.[7,8]

Antihelminthic treatment leads to degradation of encysted larvae by making the larvae recognizable to the host's immune system. During treatment, the host immune response against the cyst often leads to cerebral edema and consequently seizures. Corticosteroids are routinely used to control edema and antiepileptic drugs (AEDs) are often used for prevention of seizures, and both are commonly coadministered during antihelminthic treatment of NC.[4,7] The objective of this review is to evaluate the current evidence for common drug interactions with albendazole and praziquantel during treatment of NC and to identify gaps in the existing scientific literature.

Pharmacokinetics of Albendazole

Albendazole has low bioavailability after oral administration, which may be related to poor absorption due to limited solubility.[9] After absorption, albendazole is subject to

rapid and extensive first-pass metabolism into the chiral metabolite, albendazole sulfoxide, which is the entity responsible for its cysticidal activity.[10] The (+),-enantiomer of albendazole sulfoxide has the greatest pharmacologic activity against *T. solium*.[11] Albendazole is subject to high intrinsic clearance[12] which may be a result of poor absorption, extensive first pass metabolism, or a combination of these factors. Albendazole sulfoxide also exhibits a degree of plasma protein binding (62%-72%).[13] Flavin-containing monooxygenases and cytochrome P450 (CYP) 3A isoenzymes are responsible for the first pass hepatic metabolism of albendazole into albendazole sulfoxide.[10] Albendazole sulfoxide is then converted into an inactive metabolite, albendazole sulfone, a process that is also mediated by CYP450; however, the precise isoforms responsible for this process remain unclear.[10,14,15] Because of the involvement of CYP 3A isoenzymes in the formation of the active metabolite, it is not surprising that inhibitors of CYP 3A, such as ritonavir, as well as inducers, such as phenytoin, may influence plasma concentrations of albendazole sulfoxide.[16,17]

The pharmacokinetics of albendazole are subject to high interpatient variability. The population pharmacokinetics of albendazole were prospectively evaluated in a study by Castro et al. in which 90 patients with NC received a standard regimen of 30 mg/kg/day for 8 days.[18] In about one-quarter of patients, the bioavailability of albendazole was only 28%, compared with complete bioavailability modeled in roughly three-quarters of patients. This substantial difference in bioavailability between this subpopulation and the rest of the study participants was not accounted for by covariates such as age, sex, or creatinine clearance, and concomitant drugs. Concurrent diet was not described in this

study, which may have affected albendazole sulfoxide plasma concentrations. The low exposures of albendazole sulfoxide in a substantial subpopulation observed in this study should be considered as a possible reason for the suboptimal efficacy of albendazole in some patients with NC.[18]

Pharmacokinetics of Praziquantel

Praziquantel is a highly lipophilic molecule and is well-absorbed from the gastrointestinal tract.[19] It is administered as a racemic mixture, with (–)-(R)-praziquantel being the pharmacologically active enantiomer.[20] Praziquantel is metabolized by hepatic CYP 1A, CYP 3A and CYP 2C isoenzymes into inactive hydroxylated compounds.[12] Similar to albendazole, praziquantel is also subject to high intrinsic clearance, but in contrast, this is probably due to its extensive first pass metabolism, rather than poor absorption. Although its distribution has not been extensively studied, it has been reported that praziquantel is 80% to 85% bound by plasma proteins.[13] The metabolism of praziquantel makes certain drug-drug interactions easier to assess because unlike albendazole for which CYP450 isoenzymes are involved in the formation of both the active and inactive metabolite, with praziquantel, CYP450 isoenzymes are only involved in the conversion of the active into the inactive metabolite. Drugs that inhibit CYP 3A isoenzymes, such as ketoconazole, and drugs that induce CYP 3A, such as rifampin, may significantly influence plasma concentrations of praziquantel.[21,22]

Drug Interactions with Antiepileptic Drugs

First generation AEDs—phenobarbital, phenytoin, and carbamazepine—are potent inducers of CYP isoenzymes, including 3A and 1A[23], of which CYP 3A isoenzymes are involved in the metabolism of both albendazole and praziquantel and 1A isoenzymes are involved in the metabolism of praziquantel. In addition, first generation AEDs have high plasma protein binding.[24] AEDs are often needed for prevention and treatment of seizures during antihelminthic treatment of NC because the inflammatory response to treatment may induce seizures and also because new onset epilepsy may have been the event that led to a diagnosis of NC. Drug-drug interaction studies have shown that there is a significant pharmacokinetic interaction between AEDs and antihelminthic agents.

Lanchote et al. evaluated the pharmacokinetic interaction between AEDs and albendazole in a study that included patients with parenchymal NC and viable cysts.[17] Patients received albendazole (7.5 mg/kg every 12 hours) for 8 days and were divided by their AED use for at least the last 3 months: no AED, phenytoin, carbamazepine, or phenobarbital. In addition, 40% of patients received dexamethasone, during treatment with albendazole for control of cerebral edema. Despite the high interindividual variability of albendazole metabolite concentrations in the plasma, all 3 antiepileptic drugs significantly reduced the mean maximum concentration (C_{max}) and area under the concentration-time curve (AUC) of (+),-albendazole sulfoxide after 8 days of therapy (Table 1). Reduced bioavailability may have been explained by increased extraction upon first pass metabolism secondary to the CYP inducing effects of AEDs on albendazole. However, the role of plasma protein binding should also be considered because phenytoin, carbamazepine, and phenobarbital have high plasma protein binding

(>80%)[24] and albendazole sulfoxide also binds to plasma proteins, albeit to a smaller degree (62% to 72%).[13] Because half-life was also significantly reduced when AEDs were coadministered with albendazole, it is a possibility that the unbound fraction of albendazole sulfoxide was increased due to competition for plasma proteins with AEDs and free albendazole sulfoxide was subsequently cleared extensively, leading to a reduction in half-life. In addition, it is known that dexamethasone can significantly increase plasma concentrations of albendazole sulfoxide[25,26] and although a subgroup analysis was not described, this did not appear to counteract effect of AEDs on reducing plasma concentrations of albendazole sulfoxide.[17]

As is the case with albendazole, plasma concentrations of praziquantel are significantly reduced by coadministration of AEDs (Table 1). In a study by Bittencourt et al., epileptic patients without NC who were stable on monotherapy of phenytoin or carbamazepine for at least 6 months and healthy controls both received a single dose of praziquantel (25 mg/kg).[27] Unlike the study by Lanchote et al. that evaluated albendazole, the pharmacokinetics of specific enantiomers of praziquantel were not evaluated. The AUC and C_{max} of praziquantel in patients receiving carbamazepine or phenytoin were significantly lower compared with patients not receiving AEDs. T_{max} was not significantly different between groups, suggesting that the drug interaction was not related to absorption. Aside from induction of first-pass hepatic metabolism, it is a possibility that phenytoin and carbamazepine may also play a role in displacing praziquantel from plasma protein binding sites, as with albendazole, leading to an increase in the unbound fraction of praziquantel and subsequent extensive clearance.[27]

Cimetidine has been used in some cases to counteract the drug interaction between praziquantel and AEDs;[28] however, this approach has not been evaluated prospectively.

An important limitation of these studies is that they were not crossover studies[17,27], so it difficult to account for interpatient pharmacokinetic variability, which is particularly high with albendazole.[18] Additionally, CYP 3A isoenzyme activity is variable and thus, different levels of CYP 3A induction would be expected among different patients.

In clinical trials evaluating antihelminthic treatment of NC, primarily phenytoin and carbamazepine have been used for seizure control.[7,8] The use of newer AEDs, which do not induce CYP enzymes and have lower plasma protein binding, may warrant further evaluation for use during treatment of NC to see if their use has any differential effect on cyst reduction. There is increasing clinical experience and evidence with newer AEDs[29]; however, there is little published data on their use specifically in NC. An additional consideration relevant in the context of treating NC is that newer AEDs may not be on Essential Medicines Lists in endemic countries and their costs may be prohibitive for many patients in low resource settings.[30]

Drug Interactions with Corticosteroids

Corticosteroids are subject to a variety of drug-drug interactions related to their metabolism by CYP isoenzymes.[31] For example, AEDs can significantly reduce plasma concentrations of prednisolone and methylprednisolone.[31] Corticosteroids are routinely administered during antihelminthic treatment to reduce the cerebral edema that results

from degenerating cysts. However, it appears that albendazole and praziquantel interact differently with dexamethasone.

A study by Jung et al. demonstrated that coadministration of dexamethasone significantly increased plasma concentrations of albendazole sulfoxide in patients with NC.[25] In this study, albendazole was given at a dose of 15 mg/kg divided into three daily doses for 8 days, followed by another 8 days when dexamethasone 8 mg was given with each dose of albendazole. The mean plasma concentration of albendazole sulfoxide during the first 8 days without concurrent dexamethasone was 728 ng/mL (range 169 ng/mL to 2268 ng/mL), which increased by 56% to a mean of 1253 ng/mL (range 306 ng/mL to 1934 ng/mL) during the last 8 days when dexamethasone was given concurrently. Of the 8 patients in this study, all patients except one had increased albendazole sulfoxide plasma concentrations when dexamethasone was added (range: -9% to 592%).[25] A larger sample size may have helped determine if this increase in albendazole sulfoxide plasma concentrations could be at least partially explained by interpatient variability.

Similarly, a study that compared an 8-day course of albendazole alone, albendazole with dexamethasone, and albendazole with dexamethasone and cimetidine in patients with NC found that dexamethasone significantly increased plasma concentrations of albendazole sulfoxide.[26] The group receiving albendazole with dexamethasone had a median steady-state AUC of albendazole sulfoxide that was significantly higher compared with the group that received albendazole monotherapy (4.7 mcg/h/mL vs. 2.3 mcg/h/mL; $P<.05$). This study also evaluated oral clearance (CL/F) of albendazole sulfoxide, which was

roughly one-third lower in participants receiving concurrent dexamethasone compared with patients receiving albendazole monotherapy (1.05 L/h/Kg vs. 3.02 L/h/Kg; $P<.05$). The lower clearance observed with concurrent dexamethasone suggests that dexamethasone increases plasma concentrations of albendazole sulfoxide by decreasing its clearance, rather than affecting its formation. The pharmacokinetic profile of albendazole sulfoxide was similar between the group receiving cimetidine with albendazole and dexamethasone and the group receiving albendazole and dexamethasone alone, suggesting that the increase in plasma concentrations was mainly due to the addition of dexamethasone. As this was not a crossover study, it is also important to consider the role of differences in drug disposition between patients as a potential source of bias.[26]

Unlike with albendazole, dexamethasone may significantly reduce plasma concentrations of praziquantel. In a study by Vazquez et al., 8 patients with parenchymal NC began to receive dexamethasone half-way through a 2 week course of praziquantel.[32] Simultaneous administration of both drugs significantly reduced mean praziquantel concentrations at steady state compared to when praziquantel was administered alone (3.1 ± 0.1 mcg/mL vs 1.6 ± 0.6 mcg/mL; $P<.001$). This was a consistent effect, with reductions in praziquantel plasma concentrations observed in all patients. The potential mechanism for this interaction remains unclear, as clearance was not evaluated in this study.[32]

In our review of the literature, only drug-drug interaction studies with dexamethasone were identified. In clinical practice, other agents such as prednisolone are also often used. Because the mechanism of the drug interactions with dexamethasone is unclear, the potential effect of other corticosteroids on the pharmacokinetics of albendazole and praziquantel is unknown and should be studied.

Drug Interactions with Histamine-2 Antagonists and Proton Pump Inhibitors

Histamine-2 antagonists and proton pump inhibitors are often used to prevent the gastric toxicity of corticosteroids in patients being treated for NC. As these agents can increase gastric pH, their use can significantly alter the absorption of drugs that are absorbed only at specific pH levels. In the literature, we only identified studies that evaluate drug-drug interactions between albendazole and praziquantel with cimetidine. Additional studies are needed that evaluate interactions with more commonly used histamine-2 antagonists such as ranitidine, and proton pump inhibitors.

The absorption of albendazole may be pH dependent, as demonstrated by a drug interaction study with cimetidine (a histamine-2 antagonist and CYP 3A inhibitor) and grapefruit juice (a CYP 3A inhibitor).[33] In this study, administration of grapefruit juice alone with albendazole increased albendazole sulfoxide C_{max} and AUC significantly, suggesting that albendazole is subject to mucosal CYP 3A isoenzyme metabolism. The role of grapefruit juice in activating P-glycoprotein (P-gp) to modulate the bioavailability of albendazole has also been considered; however, it does not appear that albendazole interacts with P-gp.[34] In contrast, concurrent administration of grapefruit juice and

cimetidine decreased the C_{max} of albendazole from 0.8 ± 0.5 mg/L to 0.4 ± 0.3 mg/L (*P*= .022) and $AUC_{0\text{-inf}}$ from 6.5 ± 5.1 mg/h/L to 3.5 ± 1.9 mg/h/L (*P*=.118) compared with grapefruit juice alone. Although it may seem paradoxical that coadministration of two CYP 3A isoenzyme inhibitors decreases plasma concentrations of a CYP 3A substrate, this reduction in C_{max} may actually be the result of inhibition of gastric acid secretion by cimetidine, suggesting that absorption of albendazole is pH dependent.[33] However, in the absence of a comparator group that only received cimetidine, this hypothesis is difficult to support because cimetidine has not always shown a significant pharmacokinetic effect when added to albendazole.[26]

Unlike albendazole, it does not appear that the absorption of praziquantel is pH dependent. In a crossover study evaluating the interaction between cimetidine and praziquantel, coadministration of both agents after 3 doses increased mean C_{max} from 1.8 ± 0.7 mcg/mL to 3.7 ± 1.5 mcg/mL, mean AUC from 6.6 ± 2.5 mcg/mL/h to 11.5 ± 4.6 mcg/mL/h and increased mean $t_{1/2}$ from 1.8 ± 0.5 hours to 2.4 ± 0.6 hours (*P*<.05 for all comparisons).[35] T_{max} did not significantly increase, suggesting that the addition of cimetidine did not affect the absorption of praziquantel and that this drug-drug interaction was mediated by CYP 3A inhibition.[35]

Drug Interactions with Food

Concurrent diet may be an important consideration during antihelminthic treatment because food can have a significant effect on plasma concentration of both albendazole and praziquantel. A two-way crossover study of 16 healthy volunteers evaluated the

effect of a high-fat meal (61.1 g total fat) with a single 800 mg dose of albendazole.[36] Compared with the fasting state, a high-fat meal increased albendazole sulfoxide C_{max} from 0.26 ± 0.1 mcg/mL to 1.8 ± 0.6 mcg/mL, $AUC_{0\text{-}inf}$ from 5.1 ± 2.8 mcg/h/mL to 29.4 ± 14.6 mcg/h/mL, and T_{max} from 3.2 ± 1.1 hours to 5.1 ± 1.6 hours (P<.05 for all comparisons). In contrast, CL/F was reduced from 0.2 ± 0.2 mL/h (fasting) to 0.04 ± 0.02 mL/h (high fat meal), as well as volume of distribution (Vd/F), 3.0 ± 1.9 mL (fasting) to 0.4 ± 0.2 mL (high fat meal) (P<.05 for both comparisons). Although a high fat meal increased plasma concentrations of albendazole sulfoxide, there was significant variability in pharmacokinetics among the participants of this study. This variability may be influenced by additional factors, such as differences in gastric pH and drug metabolism.[36]

Similar to albendazole, concomitant administration of food with praziquantel has a significant effect on its plasma concentrations. In a study by Castro et al., healthy volunteers were randomly assigned to receive praziquantel 1800 mg with a high fat meal, a high carbohydrate meal, or after 10 hours of fasting.[37] Mean C_{max} was 318.8 ± 227.2 ng/mL among fasting participants compared with 1095.4 ± 780.0 ng/mL for participants receiving the high fat meal and 1962.2 ± 779.8 ng/mL for participants receiving the high carbohydrate meal (P<.05 for both comparisons). Mean $AUC_{0\text{-}8}$ was 882.3 ± 416.8 ng/h/mL among fasting participants compared with 2474.6 ± 1166.0 ng/h/mL for participants receiving the high fat meal and 3276.2±969.7 ng/h/mL for participants receiving the high carbohydrate meal (P<.05 for both comparisons). Since the high fat meal also contained a high amount of carbohydrates, it is possible that it was the

carbohydrates and not the fats that caused the increase in the bioavailability of praziquantel.[37]

The mechanisms for the drug-food interactions with albendazole and praziquantel are unclear. In the case of albendazole, the increased plasma concentrations may have been a result of increased intestinal absorption, because a fatty meal increased the plasma concentrations of the active metabolite, albendazole sulfoxide. However, plasma concentrations of the parent compound were not evaluated and thus other processes, such as increased lymphatic absorption, cannot be ruled out. With praziquantel, the mechanism for this interaction is even less clear and may result from many potential processes including increased intestinal absorption, increased lymphatic absorption, or enhanced lipoprotein binding. As NC affects many diverse endemic regions, it is important to also consider local diet when interpreting these studies.

Clinical Relevance of Plasma Concentrations of Albendazole and Praziquantel During Treatment of NC

Based on the available literature, both unidentified causes of pharmacokinetic variability and drug interactions may significantly affect plasma concentrations of albendazole and praziquantel. Monitoring of plasma concentrations of albendazole and praziquantel is possible;[20] however, the clinical relevance of trough and peak plasma concentrations of either drug has not been established. Even if routine therapeutic drug monitoring is a possibility, it may not be realistic for clinical practice in some low resource primary care settings.

The overarching issue with drug interactions during the treatment of NC is that the clinical importance of albendazole and praziquantel plasma concentrations has not been firmly established. A study that showed a single day of high dose praziquantel compared with a standard weeklong regimen of albendazole was effective for treating NC provides some anecdotal evidence that the cysticidal activity of praziquantel may be dose dependent and therefore, plasma concentrations may be clinically important.[38] However, a study of 29 patients did not find any correlation between plasma concentrations of albendazole and praziquantel and cysticidal efficacy at 3 months.[39] What limits the generalizability of this study is that the majority of the patients with an available 3 month CT scan had complete disappearance of cysts, which is a finding that has not been observed in large randomized controlled trials.[7,8] Plasma concentrations of albendazole and praziquantel should be taken and analyzed in future, large clinical trials to provide stronger evidence to evaluate the validity of a causal relationship between antihelminthic plasma concentrations and reduction in cysts.

Conclusions and Future Directions

Based on the available literature, there are significant route drug and food interactions during treatment of NC with albendazole and praziquantel. Given the paucity of outcome-based data, it is not possible to make evidence-based recommendations for managing drug interactions with albendazole and praziquantel in patients with NC. Studies are needed that provide evidence-based strategies for managing drug interactions in NC (e.g., increasing or reducing the dose of antihelminthic agents). Furthermore, the

clinical relevance of plasma concentrations of albendazole and praziquantel during treatment of NC needs to be determined, so that the drug interactions can be better understood and managed and current antihelminthic treatment can be optimized.

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Tables

Table 1. Effect of antiepileptic drugs on albendazole sulfoxide and praziquantel pharmacokinetics[17,27]

* *P*<.05; † *P*<.01.

	Albendazole control (n=9)	Phenytoin + albendazole (n=9)	Carbamazepine + albendazole (n=9)	Phenobarbital + albendazole (n=5)		Praziquantel control (n=10)	Phenytoin + praziquantel (n=10)	Carbamazepine + praziquantel (n=10)
Mean C_{max} (ng/mL)	807.2 (538.5-1075.9)	279.4* (171.9-386.6)	408.4* (275.9-540.8)	286.5* (39.5-612.5)		1550 (311-4735)	375† (31-1170)	122† (51-275.3)
Mean AUC (ng*h/mL)	6123.1 (3270.3-8975.9)	2115.4* (1316.7-2914.1)	3098.2* (1924.7-4271.7)	2432.4* (146.1-4718.7)		3270 (920-5780)	853† (55-1900)	318† (111-648)
Mean $t_{1/2}$ (h)	8.0 (5.8-10.2)	3.8* (2.5-5.2)	4.1* (3.0-5.2)	4.9 (1.3-8.5)		1.9 (1.4-2.4)	1.7 (0.8-2.0)	1.7 (1.2-2.6)