Am. J. Trop. Med. Hyg., 90(5), 2014, pp. 819–822
doi:10.4269/ajtmh.13-0059

Safety of the Combined Use of Praziquantel and Albendazole in the Treatment of Human Hydatid Disease

Lucía Alvela-Suárez,* Virginia Velasco-Tirado, Moncef Belhassen-Garcia, Ignacio Novo-Veleiro, Javier Pardo-Lledías, Angela Romero-Alegría, Luis Pérez del Villar, María Paz Valverde-Merino, and Miguel Cordero-Sánchez

Complejo Asistencial Universitario de Salamanca (CAUSA), Salamanca, Spain; General Hospital of Palencia "Rio Carrión," Palencia, Spain

Abstract. There is still no well-established consensus about the clinical management of hydatidosis. Currently, surgery continues to be the first therapeutic option, although treatment with anti-parasitic drugs is indicated as an adjuvant to surgery to decrease the number of relapses and hydatid cyst size. When surgery is not possible, medical treatment is indicated. Traditionally, albendazole was used in monotherapy as the standard treatment. However, combined therapy with albendazole plus praziquantel appears to improve anti-parasitic effectiveness. To date, no safety studies focusing on such combined therapy have been published for the treatment of hydatidosis. In this work, we analyze the adverse effects seen in 57 patients diagnosed with hydatidosis who were treated with praziquantel plus albendazole combined therapy between 2006 and 2010.

INTRODUCTION

Hydatidosis is a zoonosis caused by cestode worms of the genus *Echinococcus* spp. Among them, *Echinococcus granulosus* is the most important species that parasitizes humans. The relevance of this neglected parasitic disease is well known; in fact, human hydatidosis has a greater socio-economic impact than Chagas or Hansen's diseases.[1,2] *Echinococcus granulosus* has a worldwide geographical distribution and the Mediterranean basin is considered an important endemic area.[3–6] In this sense, a recent epidemiological study performed in our area (Salamanca, Spain) between 1996 and 2003 established the human incidence of hydatid disease at 10.8 per 100.000 habitants per year.[7]

Despite World Health Organization (WHO) recommendations, there is no optimal standard for the treatment of hydatidosis. This lack of consensus is possibly a result of the complexity of this neglected disease and limitations related to health care facilities.[8,9] There are basically three treatment options: surgical, percutaneous treatment, and the use of anti-parasitic drugs.[10–12] Surgery continues to be the first choice for the treatment of hydatidosis. Nevertheless, it is not the optimal therapeutic option for all patients, mainly limited by poor clinical conditions and the location of the hydatid cysts. Thus, other techniques such as PAIR (Puncture, Aspiration, Injection, and Reaspiration) have gained international recognition[13–15]; nevertheless, PAIR has several contraindications, among them the possibility of breakage or fistulation of the cysts. In addition, the location of the cyst in organs such as heart or brain means that PAIR is not always feasible. Accordingly, because of the contraindications and complications of invasive procedures, in recent years medical therapy has gained ground over the other choices.[16–18]

Medical treatment is usually indicated before surgery to diminish the size of hydatid cysts, to sterilize them, and to avoid relapses. In addition, medical treatment is the sole therapeutic option in disseminated hydatidosis. To date, the medical treatment of hydatidosis has relied on compounds belonging to the benzimidazoles family (albendazole or mebendazole); in particular, albendazole currently represents the best pharmacological option for the treatment of hydatidosis.[19–22] Over the past few decades, other anthelmintic chemotherapies such as praziquantel and nitazoxanide have also been tested against *Echinococcus* spp., but their efficacies are inferior to those of benzimidazoles.[16,23,24] Despite this, the combination of albendazole with praziquantel has shown synergistic activity against *Echinococcus* spp. In fact, observational studies suggest that the combined therapy could improve the cure rates obtained with albendazole alone[23–26]; regarding the safety of medical therapy, an increase in transaminases levels is the most frequent adverse reaction related to albendazole treatment,[27] whereas digestive symptoms are the most frequent adverse effects associated with praziquantel in monotherapy. Anaphylactic reactions related to praziquantel have also been described.[28,29] Some safety studies have focused on the co-administration of albendazole plus praziquantel in other parasitic diseases,[30–33] but no randomized clinical trials have been conducted to determine the safety of combined therapy in human echinococcosis. Therefore, the main objective of this study is to evaluate the safety and tolerability of combined treatment with praziquantel and albendazole in a group of 57 patients diagnosed with hydatidosis.

MATERIAL AND METHODS

This was a retrospective observational study. The epidemiological data and those regarding the clinical evolution of the disease were collected after a review of the medical records collected from patients diagnosed with echinococcosis. The diagnosis of hydatid disease was based on the combination of clinical assessment, serological tests, and imaging techniques (computed tomography, ultrasonography, or magnetic resonance imaging, depending on the location of the hydatid cyst and the patient's characteristics). The criteria for eligibility included patients treated with the combined treatment of albendazole and praziquantel. The study was conducted between January 2006 and July 2010 in the University Hospital of Salamanca, located in Western Spain. This center is a tertiary care hospital attending a population of 350,000 individuals. A descriptive statistical analysis was carried out using the SPSS Statistical Package (SPSS Inc., Chicago, IL). The

*Address correspondence to Lucía Alvela-Suárez, Paseo de San Vicente sn, Salamanca, 37007. E-mail: luciaalvela@hotmail.com

TABLE 1

Clinical and epidemiological data of patients infected with *Echinococcus granulosus*

Patients ($N = 57$)	
Age (mean ± SD)	52.7 ± 16.7
Percentage of women patients (%)	35 (61.4)
Location of cyst	
Liver	42 (73.7%)
Lung	3 (5.3%)
Various locations	12 (21.1%)
Complications of hydatid cysts	46 (80.7%)
Fistulization	21 (36.8%)
Compression of structures*	16 (28.1%)
Superinfection†	8 (14%)
Anaphylactic shock	1 (1.7%)
Treatment ABZ+PZQ‡	
Before surgery	5 (8.8%)
After surgery	20 (50.9%)
Before and after surgery	16 (28.1%)
Only chemotherapy	7 (12.2%)

*Cyst complicated with obstruction biliary, obstruction bronchial, etc.
†Cyst complicated with other microorganism mainly bacterial and fungal.
‡Albendazol and praziquantel.

data were described as means ± SD or frequency and percentage when appropriate.

RESULTS

Five hundred and fifty-two patients were newly diagnosed with hydatidosis between January 2006 and July 2010. Of them, 57 (37.5%) were treated with albendazole plus praziquantel; the clinical–epidemiological data of these 57 patients are shown in Table 1. Average age was 52.7 ± 16.7 years and 35 (61.4%) patients were female. The liver was the organ most frequently affected in 42 cases (73.7%), followed by the lung in 3 cases (5.3%). In addition, 31 patients (54.4%) had more than one cyst. Of importance, a high number of patients 46 (80.7%) had a complication related to hydatid cysts: 21 (36.8%) cases showed fistulation (17 biliary, 2 bronchial, 1 vascular, and 1 subcutaneous), 16 cases (28.1%) had compression of structures, 8 (14%) cases had a superinfection of the hydatid cysts, and 1 (1.7%) patient underwent an anaphylactic reaction, with shock.

Treatment with albendazol plus praziquantel was associated with surgery in 50 (87.7%) of the cases: specifically, 5 (8.8%) patients received the combined therapy before surgery, 29 (50.9%) patients received the combined therapy after surgery, and 16 (28.1%) patients received the medical treatment both before and after surgery. The remaining 7 (12.2%) patients were excluded for intervention because of their age, their underlying pathology, or the presence of multiple hydatid cysts. The drug administration schedule was 400 mg q12h for albendazole, whereas the dosage for praziquantel was 20–75 mg/kg/day, depending on the patient's weight, as shown in Table 2. The average duration of treatment was 68 weeks (range 1–436 weeks) and 37 (64.9%) patients received combined treatment of more than 1 year. Four (7%) patients were lost to follow-up; 2 (3.5%) patients died because of primary complications of their hydatid cyst; 17(29.8%) patients continued the medical therapy with albendazol plus praziquantel, and 3 (5.3%) patients continued the treatment with albendazol alone.

TABLE 3

Adverse effects related with the combined treatment (praziquantel and albendazole)

Adverse effects	Number of patients
Digestive effects	6 (10.5%)
Diarrhea	3 (5.2%)
Vomiting and abdominal pain	2 (3.5%)
Hypertransaminasemia	1 (1.7%)
Neurological effects	2 (3.5%)
Migraine	1 (1.7%)
Dysgeusia and dysosmia	1 (1.7%)

The safety analysis included self-reporting of adverse events, hemograms, and biochemistry before and after treatment. Only 8 (14%) patients reported some mild adverse effects (Table 3). The most frequent were digestive; specifically 3 (5.2%) patients developed diarrhea, 2 (3.5%) cases reported vomiting, and 1 (1.7%) patient presented a mild hypertransaminasemia (alanine aspartate aminotransferase maximum 74 U/L and alanine aminotransferase maximum 154 U/L), followed by neurological problems such as headaches in 1 (1.7%) and dysgeusia in 1 (1.7%) patient. No clinically relevant changes in the hematological results were detected along the treatment period. The adverse events tended to occur within the first 2 weeks after start of treatment. In these cases, the adverse effects disappeared after the withdrawal of albendazole plus praziquantel or praziquantel; in these medical therapy was continued, maintaining albendazole alone.

DISCUSSION

Despite the efforts made by the WHO to define a new classification of patients to homogenize and optimize studies addressing human hydatidosis,[34] the results expected have

TABLE 2

Outcome measures of patients infected with *Echinococcus* spp. included in the combined treatment protocol

No. of cases	Praziquantel	Albendazole	Treatment time in weeks median and range	Side effects no. of cases (%)	Clinical evolution
20	1,200 mg q12h* 2,400	400 mg bid	68 R = 437 (9–436)	3 (15.0%)	Improvement 8 (40%) Equal 8 (40%) Worsening 1 (5.0%)
16	600 mg q8h** 1,800	400 mg bid	62 R = 427 (9–436)	1 (6.3%)	Improvement 9 (56.3%) Equal 6 (37.5%) Worsening 1 (6.3%)
4	600 mg q12h 1,200	400 mg bid	60 R = 68 (26–94)	0	Improvement 2 (50.0%) Equal 2 (50.0%)
3	1,200 mg q8h 3,600	400 mg bid	216 R = 204 (66–270)	0	Equal 3 (100%)
1	1,200 mg-600 mg-1,200 mg 3,000	400 mg bid	162 R = 0	0	Improvement 1 (100%)
13	Unknown dose	400 mg bid	58 R = (1–108)	4 (30.8%)	Improvement 6 (46.2%) Equal 5 (38.5%)

not emerged. Presently, there are no common clinical guidelines or an established consensus for the clinical management of hydatidosis. Among other reasons, this lack of consensus could be caused by the considerable difficulty involved in dealing with this cestode in terms of its slow evolution and clinical variability. This strong heterogeneity in the medical management of the disease prompted us to evaluate a treatment protocol combining albendazole and praziquantel. The medical treatment was initiated before surgery, and was held for up to 1 year. If the clinical, analytical, and radiological controls were negative, the medical therapy was suspended 1 year after the start of the combined therapy.

The drugs classically used against *E. granulosus* are the benzimidazoles. This family of compounds began to be used at the beginning of the 70s.The first drug used for hydatidosis treatment was mebendazole. However, in the 80s this drug was replaced by albendazole because of its better bioavailability.[8,19–21] The mechanism of anti-parasitic action of the benzimidazoles is based on a decrease in the recapture of glucose and their union to β-tubulin, which generates metabolic and structural alterations in the parasite, leading to its death.[19] Hydatid cysts not affordable by surgery require a plasma concentration of 100 ng/mL of albendazole for months or years for the necessary anthelmintic effect to be achieved.[35] Medical treatment implemented at doses between 800 and 1,200 mg/day (10–20 mg/kg day) for 3–4 months achieves cure rates of hepatic cysts that vary from 28.5% to 43%, with a rate of relapse between 3% and 22%, whereas the cure rates of pulmonary hydatid cysts reach 73%. In addition, as previously indicated medical treatment with albendazole before surgery allows relapses to be reduced.[36,37]

Other anti-parasitic drugs have been tested in combination with benzimidazoles with a synergic action. Although there are no comparative randomized studies exploring treatment with albendazole in monotherapy versus combined therapy with albendazole plus praziquantel in patients without surgery, it appears that the combined therapy could improve the results obtained with albendazole alone.[17,18,23–26,38] In addition, treatment with praziquantel plus albendazole before surgery could be more efficient as regards reducing relapse rates in comparison with albendazole monotherapy.[23] To date, there are no published randomized clinical trials comparing both therapeutic strategies. Moreover, only a few studies in the literature report the use of the combined therapy for the treatment of hydatidosis, and these are based on small series. Only one randomized assay performed in sheep with natural echinococcosis infection showed that the benzimidazoles with or without praziquantel had greater efficacy than placebo administration. However, no differences were observed between the monotherapy and combined treatment groups and evidently no adverse effects were described.[39] Furthermore, it is possible that medical treatment alone, when surgery is not feasible, could reduce and even disappear the hydatid cysts; in fact, some series suggest that prolonged medical treatment could be more advantageous than surgery.[40]

Some safety studies have focused on the co-administration of albendazole and praziquantel in other parasitic diseases[30–33]; however, there are no safety studies for combined treatment with these drugs in human echinococcosis. Thus, experience related to the safety of praziquantel is based on its use in other pathologies requiring treatment of much shorter times.[41–43] By contrast, the medical treatment of hydatidosis is more prolonged and in this sense our series of cases even surpassed 1 year of treatment. It is interesting to note that the long-term side effects observed in this work were mild and disappeared after the withdrawal of praziquantel. The most frequent adverse reactions affected the digestive system and included nausea, vomiting, and diarrhea, as previously described by other authors reporting studies in which praziquantel was used in other parasitic diseases.[29,44] Interestingly, one of our patients developed dysgeusia and dysosmia; this side effect is not included in the technical record of praziquantel, and to our knowledge this is the first time it has been observed as a side effect related to praziquantel.[45] New drugs are also being tested, in particular in disseminated hydatidosis with multiple cysts or bone affectation, which makes surgery impossible. The use of nitazoxanide in combination with albendazole, with or without praziquantel, appears to be useful in this type of case.[16,46] In our series there was an obvious selection bias, because all patients were hospitalized and no outpatients were included (who generally present a less aggressive hydatidosis), and of course without bearing in mind carriers of asymptomatic of hydatid cysts, which have not even been diagnosed. This would suggest the existence of an over dimension of severe cases in our series. In any case, this would not affect our conclusions regarding tolerance and the appearance of possible side effects with this medication.

CONCLUSIONS

According to our experience, the adverse effects related to praziquantel plus albendazole combined therapy are mild and infrequent, being reversible after treatment has been withdrawn. Thus, the use of this combined therapy seems to be feasible and safe for the treatment of patients with hydatidosis, although further clinical studies are necessary to confirm these observations.

Received January 28, 2013. Accepted for publication December 17, 2013.

Published online March 10, 2014.

Authors' addresses: Lucía Alvela-Suárez, Virginia Velasco-Tirado, and Ignacio Novo-Veleiro, CAUSA, Internal Medicine, Salamanca, Spain, E-mails: luciaalvela@hotmail.com, virvela@yahoo.es, and ignacio.novo.veleiro@gmail.com. Moncef Belhassen-Garcia, CAUSA, Internal Medicina and Infectious Diseases, Salamanca, Spain, E-mail: mbelhassen@hotmail.com. Javier Pardo-Lledías, General Hospital of Palencia "Río Carrión" - Internal Medicine, Palencia, Spain, E-mail: javipard2@hotmail.com. Angela Romero-Alegría, CAUSA, Internal Medicine, Salamanca, Spain, E-mail: aralegria@yahoo.es. Luis Pérez del Villar, University of Salamanca - CIETUS, IBSAL, Salamanca, Spain, E-mail: luipmoro@usal.es. María Paz Valverde-Merino, CAUSA, Pharmacy Service, Salamanca, Spain, E-mail: mpvalverde@saludcastillayleon.es. Miguel Cordero-Sánchez, CAUSA, Infectious Diseases, Salamanca, Spain, E-mail: magnus@usal.es.

REFERENCES

1. Budke CM, Deplazes P, Torgerson PR, 2006. Global socioeconomic impact of cystic echinococcosis. *Emerg Infect Dis 12:* 296–303.
2. Hotez PJ, Molyneux DH, Fenwick A, Kumaresan J, Sachs SE, Sachs JD, Savioli L, 2007. Control of neglected tropical diseases. *N Engl J Med 357:* 1018–1027.
3. Seimenis A, 2003. Overview of the epidemiological situation on echinococcosis in the Mediterranean region. *Acta Trop 85:* 191–195.
4. Sotiraki S, Himonas C, Korkoliakou P, 2003. Hydatidosis-echinococcosis in Greece. *Acta Trop 85:* 197–201.
5. Lorenzini R, Ruggieri A, 1987. Distribution of echinococcosis/hydatidosis in Italy. *J Helminthol 61:* 261–267.

6. Rojo-Vazquez FA, Pardo-Lledias J, Francos-Von Hunefeld M, Cordero-Sanchez M, Alamo-Sanz R, Hernandez-Gonzalez A, Brunetti E, Siles-Lucas M, 2011. Cystic echinococcosis in Spain: current situation and relevance for other endemic areas in Europe. *PLoS Negl Trop Dis 5:* e893.
7. Pardo J, Muro A, Galindo I, Cordero M, Carpio A, Siles-Lucas M, 2005. Hydatidosis in the province of Salamanca (Spain): should we let down our guard? *Enferm Infecc Microbiol Clin 23:* 266–269.
8. Vuitton DA, 2009. Benzimidazoles for the treatment of cystic and alveolar echinococcosis: what is the consensus? *Expert Rev Anti Infect Ther 7:* 145–149.
9. WHO, 1996. Guidelines for treatment of cystic and alveolar echinococcosis in humans. WHO Informal Working Group on Echinococcosis. *Bull World Health Organ 74:* 231–242.
10. Menezes da Silva A, 2003. Hydatid cyst of the liver-criteria for the selection of appropriate treatment. *Acta Trop 85:* 237–242.
11. Smego RA Jr, Sebanego P, 2005. Treatment options for hepatic cystic echinococcosis. *Int J Infect Dis 9:* 69–76.
12. Silva MA, Mirza DF, Bramhall SR, Mayer AD, McMaster P, Buckels JA, 2004. Treatment of hydatid disease of the liver. Evaluation of a UK experience. *Dig Surg 21*: 227–233, discussion 233–234.
13. Pelaez V, Kugler C, Correa D, Del Carpio M, Guangiroli M, Molina J, Marcos B, Lopez E, 2000. PAIR as percutaneous treatment of hydatid liver cysts. *Acta Trop 75:* 197–202.
14. Ustunsoz B, Akhan O, Kamiloglu MA, Somuncu I, Ugurel MS, Cetiner S, 1999. Percutaneous treatment of hydatid cysts of the liver: long-term results. *AJR Am J Roentgenol 172:* 91–96.
15. Filice C, Brunetti E, Bruno R, Crippa FG, 2000. Percutaneous drainage of echinococcal cysts (PAIR–puncture, aspiration, injection, reaspiration): results of a worldwide survey for assessment of its safety and efficacy. WHO-Informal Working Group on Echinococcosis-Pair Network. *Gut 47:* 156–157.
16. Perez-Molina JA, Diaz-Menendez M, Gallego JI, Norman F, Monge-Maillo B, Ayala AP, Lopez-Velez R, 2011. Evaluation of nitazoxanide for the treatment of disseminated cystic echinococcosis: report of five cases and literature review. *Am J Trop Med Hyg 84:* 351–356.
17. Mohamed AE, Yasawy MI, Al Karawi MA, 1998. Combined albendazole and praziquantel versus albendazole alone in the treatment of hydatid disease. *Hepatogastroenterology 45:* 1690–1694.
18. Yasawy MI, al Karawi MA, Mohamed AR, 1993. Combination of praziquantel and albendazole in the treatment of hydatid disease. *Trop Med Parasitol 44:* 192–194.
19. El-On J, 2003. Benzimidazole treatment of cystic echinococcosis. *Acta Trop 85:* 243–252.
20. Falagas ME, Bliziotis IA, 2007. Albendazole for the treatment of human echinococcosis: a review of comparative clinical trials. *Am J Med Sci 334:* 171–179.
21. Stojkovic M, Zwahlen M, Teggi A, Vutova K, Cretu CM, Virdone R, Nicolaidou P, Cobanoglu N, Junghanss T, 2009. Treatment response of cystic echinococcosis to benzimidazoles: a systematic review. *PLoS Negl Trop Dis 3:* e524.
22. Horton RJ, 1997. Albendazole in treatment of human cystic echinococcosis: 12 years of experience. *Acta Trop 64:* 79–93.
23. Cobo F, Yarnoz C, Sesma B, Fraile P, Aizcorbe M, Trujillo R, Diaz-de-Liano A, Ciga MA, 1998. Albendazole plus praziquantel versus albendazole alone as a pre-operative treatment in intra-abdominal hydatisosis caused by *Echinococcus granulosus*. *Trop Med Int Health 3:* 462–466.
24. Haralabidis S, Diakou A, Frydas S, Papadopoulos E, Mylonas A, Patsias A, Roilides E, Giannoulis E, 2008. Long-term evaluation of patients with hydatidosis treated with albendazole and praziquantel. *Int J Immunopathol Pharmacol 21:* 429–435.
25. Jamshidi M, Mohraz M, Zangeneh M, Jamshidi A, 2008. The effect of combination therapy with albendazole and praziquantel on hydatid cyst treatment. *Parasitol Res 103:* 195–199.
26. Salto E, Juarez E, Roiz MP, Abad J, 1991. Combined chemotherapy (mebendazole plus praziquantel) in patients with hydatidosis. *Enferm Infecc Microbiol Clin 9:* 527–529.
27. Jevtic M, Mikic D, Arsic-Komljenovic G, Stankovic N, Ristanovic E, Sjenicic G, Janicijevic-Hudomal S, 2008. Adverse effects of long term, continual administration of high doses of albendazole in the treatment of echinococcal disease. *Vojnosanit Pregl 65:* 539–544.
28. Shen C, Choi MH, Bae YM, Yu G, Wang S, Hong ST, 2007. A case of anaphylactic reaction to praziquantel treatment. *Am J Trop Med Hyg 76:* 603–605.
29. el-Hawey AM, Massoud AM, el-Rakieby A, Rozeik MS, Nassar MO, 1990. Side effects of praziquantel in bilharzial children on a field level. *J Egypt Soc Parasitol 20:* 599–605.
30. Lima RM, Ferreira MA, de Jesus Ponte Carvalho TM, Dumet Fernandes BJ, Takayanagui OM, Garcia HH, Coelho EB, Lanchote VL, 2011. Albendazole-praziquantel interaction in healthy volunteers: kinetic disposition, metabolism and enantioselectivity. *Br J Clin Pharmacol 71:* 528–535.
31. Namwanje H, Kabatereine N, Olsen A, 2011. A randomized controlled clinical trial on the safety of co-administration of albendazole, ivermectin and praziquantel in infected schoolchildren in Uganda. *Trans R Soc Trop Med Hyg 105:* 181–188.
32. Kaur S, Singhi P, Singhi S, Khandelwal N, 2009. Combination therapy with albendazole and praziquantel versus albendazole alone in children with seizures and single lesion neurocysticercosis: a randomized, placebo-controlled double blind trial. *Pediatr Infect Dis J 28:* 403–406.
33. Mohammed KA, Haji HJ, Gabrielli AF, Mubila L, Biswas G, Chitsulo L, Bradley MH, Engels D, Savioli L, Molyneux DH, 2008. Triple co-administration of ivermectin, albendazole and praziquantel in Zanzibar: a safety study. *PLoS Negl Trop Dis 2:* e171.
34. WHO, 2003. International classification of ultrasound images in cystic echinococcosis for application in clinical and field epidemiological settings. *Acta Trop 85:* 253–261.
35. Witassek F, Burkhardt B, Eckert J, Bircher J, 1981. Chemotherapy of alveolar echinococcosis. Comparison of plasma mebendazole concentrations in animals and man. *Eur J Clin Pharmacol 20:* 427–433.
36. Morris DL, Taylor DH, 1988. Optimal timing of post-operative albendazole prophylaxis in *E. granulosus*. *Ann Trop Med Parasitol 82:* 65–66.
37. Gollackner B, Langle F, Auer H, Maier A, Mittlbock M, Agstner I, Karner J, Langer F, Aspock H, Loidolt H, Rockenschaub S, Steininger R, 2000. Radical surgical therapy of abdominal cystic hydatid disease: factors of recurrence. *World J Surg 24:* 717–721.
38. Gavidia CM, Gonzalez AE, Barron EA, Ninaquispe B, Llamosas M, Verastegui MR, Robinson C, Gilman RH, 2010. Evaluation of oxfendazole, praziquantel and albendazole against cystic echinococcosis: a randomized clinical trial in naturally infected sheep. *PLoS Negl Trop Dis 4:* e616.
39. Morris DL, Richards KS, Clarkson MJ, Taylor DH, 1990. Comparison of albendazole and praziquantel therapy of *Echinococcus granulosus* in naturally infected sheep. *Vet Parasitol 36:* 83–90.
40. Haralabidis S, Diakou A, Frydas S, Papadopoulos E, Mylonas A, Patsias A, Roilides E, Giannoulis E, 2008. Long-term evaluation of patients with hydatidosis treated with albendazole and praziquantel. *Int J Immunopathol Pharmacol 21:* 429–435.
41. el Hawey AM, Massoud AM, el Rakieby A, Rozeik MS, Nassar MO, 1990. Side effects of praziquantel in bilharzial children on a field level. *J Egypt Soc Parasitol 20:* 599–605.
42. Jaoko WG, Muchemi G, Oguya FO, 1996. Praziquantel side effects during treatment of *Schistosoma mansoni* infected pupils in Kibwezi, Kenya. *East Afr Med J 73:* 499–501.
43. Shen C, Choi MH, Bae YM, Yu G, Wang S, Hong ST, 2007. A case of anaphylactic reaction to praziquantel treatment. *Am J Trop Med Hyg 76:* 603–605.
44. Jaoko WG, Muchemi G, Oguya FO, 1996. Praziquantel side effects during treatment of *Schistosoma mansoni* infected pupils in Kibwezi, Kenya. *East Afr Med J 73:* 499–501.
45. Alvela-Suarez L, Novo-Veleiro I, Belhassen-Garcia M, Velasco-Tirado V, Jimenez-Cabrera S, Iglesias-Gomez A, Cordero-Sanchez M, 2011. Dysgeusia as an adverse reaction to praziquantel. *Drug Chem Toxicol 35:* 116–117.
46. Winning A, Braslins P, McCarthy JS, 2009. Case report: nitazoxanide for treatment of refractory bony hydatid disease. *Am J Trop Med Hyg 80:* 176–178.