mens of praziquantel and oxfendazole were compared, with clear advantages in antiparasitic efficay for oxfendazole, given at 30 mg/kg. The last two experiments confirmed this dosage as the minimal effective dose of oxfendazole, and demonstrated that the death of cysticerci occurs along weeks, with larval viability persisting during the first four weeks after therapy. The important role played by informal pig raising in the economy of subsistence farmers is discussed. A treatment for porcine cysticercosis may be an important addition to control programs, at acceptable costs, and is especially attractive because of its cultural acceptability and its potential for sustainability.

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IMMUNOTHERAPY FOR PORCINE CYSTICERCOSIS

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INTRODUCTION

Cysticercosis is a parasitic disease that results from ingestion of *Taenia solium* tapeworm eggs. When humans ingest these microscopic eggs they may develop cysticercosis, an important cause of disability and mortality in many developing countries,[1] causing 20% of adult-onset epilepsy[2] and filling 12% of neurological hospital beds[3] in Peru. Porcine cysticercosis occurs when pigs ingest *T. solium* eggs and the resultant cysticercotic or 'measly' pork is of greatly reduced value.[4] In the Andean region of Peru, up to 60% of pigs have cysticercosis, contributing to economic hardship and malnutrition.[5] When humans eat infected pork they may develop *T. solium* tapeworms which release further eggs, contaminating the environment and completing the parasitic life-cycle.

Improvements in public health and animal husbandry have led to the virtual eradication of human and porcine cysticercosis in developed countries, but such measures are too expensive for immediate implementation in less developed areas.[6] Vaccination of healthy pigs with cysticercal antigens caused partial protection against porcine cysticercosis[7,8] but a vaccine is not available and may be difficult to implement in endemic regions. In contrast to preven-

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tive measures, an inexpensive treatment for porcine cysticercosis may be sought after and used by owners of infected pigs if it improved animal health, meat yield, and especially if it caused the degeneration of cysticerci in infected meat, thus increasing its value. Our group is evaluating treatments for porcine cysticercosis with drug therapy[9,10] and immunotherapy which may be cost-effective ways of breaking the life cycle of the parasite, preventing human as well as animal disease.

Cysticerci survive within host tissues by evading and modulating host immunity.[7,11] The rationale for immunotherapy is the observation that immunological intervention may alter this host-parasite interaction, causing destruction of cysticerci: pigs infected with two successive doses of *T. solium* eggs paradoxically developed significantly fewer cysticerci than pigs that had been infected with a single dose, implying that re-infection accelerated cysticercus degeneration and absorption.[12] Similarly, re-infection of cows infected with *T. saginata*[13,14] and of sheep infected with *T. hydatigena*[15] caused degeneration of established cysticerci. Furthermore, laboratory[16] and field studies[17] have reported that immunotherapy with cysticercal antigens caused the partial resolution of porcine cysticercosis. These encouraging results led us to further investigate the effect of immunotherapy on porcine cysticercosis in a randomized, controlled and blinded study.

MATERIALS AND METHODS

Twenty-eight privately reared, naturally parasitized pigs that were being sold for slaughter were purchased from Huancayo, a city in the Peruvian Sierra. All pigs were seropositive for cysticercosis and had palpable tongue nodules, implying heavy infection.[18] Swine cholera vaccine was given immediately after purchase, three weeks aclimatization was allowed, during which pigs were fed freely and no other medications were given. The animals were housed together, so the investigators were blind to treatment group. The study was approved by the ethical committee of the Facultad de Medicina Veterinaria of the Universidad de San Marcos.

Immunotherapy

The pigs were randomly divided into four treatment groups:

1. Membrane-enriched antigens (MA), five pigs;
2. Saline control, seven pigs;
3. Aqueous-soluble crude antigens (AA) in adjuvant, nine pigs; and
4. Adjuvant alone, seven pigs.

Group 1, MA was prepared by the method of Molinari, Meza & Tato.[16] In brief, 2,000 *T. solium* cysticerci were homogenized for three seconds, centrifuged at 1,500 g and the pellet was resuspended in 0.02 M phosphate buffer (pH 7.4) containing 0.4% sodium deoxycholate (Merck, Rahway, NJ) and deoxyribonuclease (Sigma, St Louis, MO) at 20 μg/ml and was ground in a mortar. The material was centrifuged at 30,000 g and the supernatant was removed and dialyzed against several changes of 0.02 M phosphate buffer (pH 7.0) for six days. After the material was centrifuged at 30,000 g for 20 minutes, the supernatant was lyophilized. The same amount of antigen was administered as in previous studies:[16,17] a subcutaneous injection of 0.25 mg of protein (in 0.1 ml saline) behind the ear on days one and seven. ***Group 2, saline*** administered in the same way as for group 1, as a control. In order to maximize the expected immune response, a larger dose of AA in adjuvant with a longer interval between doses was also evaluated: ***Group 3, AA in adjuvant*** was prepared by the method described by Estrada and Kuhn.[17] In brief, the supernatant was taken from 2,000 homogenized, sonicated, centrifuged cysticerci and the concentration was adjusted so that 2.4 mg was given in one ml of Freund's adjuvant (Sigma). This preparation was divided into five equal volumes that were injected into different subcutaneous sites on day one and again on day 14. Freund's complete adjuvant was used on day one, Freund's incomplete adjuvant on day 14. The cysticerci used for both MA and AA preparations were dissected from 17 pigs naturally infected in the same region as the pigs we treated with immunotherapy. ***Group 4, adjuvant alone:*** Freund's complete adjuvant alone on day one, followed by incomplete adjuvant alone on day 14, were administered in the same way as group 3.

Haematology and serology

Blood was taken from each pig immediately prior to the first vaccination, in week five and immediately prior to sacrifice for measurement of differential white cell count and electro-immunotransfer blot (EITB) assay.[20] In brief, the EITB assay detects *T. solium* specific antibodies by using seven lentil-lectin purified glycoprotein bands (molecular weight 50, 42-39, 24, 21, 18, 14 and 13 kD) commonly recognized by serum of humans and pigs with cysticercosis.[21,22] A similar immunoblot method[23] was also performed using the same AA that was administered as immunotherapy.

Necropsy

Pigs were anaesthetized and humanely killed 10-12 weeks after the first vaccination. Sections through the right psoas muscle, heart and right half of the brain were fixed in 10% buffered formalin (0.15 M, pH 7.2), dehydrated, set in parafin and stained with hematoxylin and eosin. At least three cysticerci from each of these three tissues were examined for every pig. Predetermined criteria were used by a histopathologist blind to treatment group to assess the host inflammatory response (cell density, predominant cell type, granulomatous reaction and degree of fibrosis) and the degree of inflammation of the cyst membrane, spiral canal and scolex (none, oedema, mild to severe inflammation, presence of host cells and degeneration or necrosis). Cell type was identified by morphology.

Parasite viability

The left psoas and left anconeal muscles, tongue and left half of the brain were weighed and dissected. Cysticerci were removed, graded according to macroscopic appearance and evagination was attempted using a standard protocol.[24] In brief, cysticerci were washed in sterile PBS (0.15 M, pH 7.2) supplemented with antibiotics and a fungistatic agent and then incubated in 1% pepsin (pH 2.0, 37 C) for 30 minutes to digest the cyst membrane. The cysts were then washed with PBS and incubated at 37°C in the evagination medium (1/1000 pH 8.9 trypsin solution with bile salts (Sigma)) for one hour. Cysticerci which failed to evaginate were considered not to be viable for infecting humans.[25]

Data analysis

Data were analyzed with the Statistical Package for the Social Sciences software (SPSS Inc, Chicago, USA). Associations between categorical variables were analyzed by the Fisher exact test and associations between continuous variables by the Mann Whitney and Kruskall Wallis one-way analysis of variance non-parametric tests.

RESULTS

There were no serious adverse reactions to immunotherapy. Two pigs developed a transient limp following vaccination in the fore-limb but no malaise, fever or scizures were noted.

Haematology and serology

Differential white cell count (including eosinophil count) did not change significantly during the study or differ between treatment groups. EITB with lentil-lectin purified glycoprotein and AA confirmed that all pigs were antibody positive at the start of the study and repeat lentil-lectin purified EITB testing at the end of the study did not reveal any changes. Using AA-EITB, some pigs developed new antibody bands during the study (12-13, 19, and 24 kD). Nine of 14 (64%) pigs given immunotherapy developed new bands in contrast to only one of 14 (7%) control pigs ($p<0.01$). The presence or development of one or more of these bands was not significantly related to white cell count, eosinophilia or cysticercal viability.

Necropsy

Necropsy confirmed that all pigs were heavily parasitized with *T. solium* cysticercosis. The mean (SD) number of cysticerci per kilogram dissected from the tissues of all pigs were: muscle 356 (418); tongue 70 (65); and brain 14 (18). Overall, the mean number of cysticerci/kg varied considerably between pigs and was highest for the saline control group, but there were no significant differences between treatment groups (Table 1). Some inflammation was present around all of the cysticerci examined but this was so variable, even between adjacent cysticerci, that it was not possible to correlate inflammatory changes with treatment group or cysticercal viability. In approximately half of the sections, 100-1,000 inflammatory cells were seen surrounding the cyst membrane, >1000 in a quarter, and <100 cells in slightly more than a quarter of all sections. Macrophages were the most common cell type, especially when more than 1,000 inflammatory cells were seen. Large numbers of eosinophils were also seen but predominated in less than a quarter of cases, most commonly in the presence of fewer than 100 inflammatory cells. Lymphocytes and plasma cells were seen in much smaller numbers.

Parasite viability

The macroscopic appearance of cysticerci revealed only six clearly degenerated cysticerci, all of which were found in two pigs that had been given AA in adjuvant. The percentage of cysticerci that failed to evaginate and were presumably not infective was calculated for each tissue from each pig (Table 1). Significantly fewer of the cysts from pigs given AA in adjuvant were viable compared to those from the adjuvant ($p<0.04$) or saline ($p<0.05$)

control groups. Adjuvant alone had no significant effect upon viability compared with saline. The effect of MA was not significant when compared with adjuvant, saline, or combined control groups. Immunotherapy (AA and MA groups combined) was associated with a 50% increase in the percentage of non-viable cysticerci when compared with the combined control groups ($p<0.04$). Immunotherapy was associated with a three-fold increase in the proportion of non-viable cysticerci in tongue tissue ($p<0.03$) and muscle ($p<0.06$), but there was no effect of immunotherapy detected in the brain ($p<0.9$). There were relatively few cysticerci in brain tissue and these were of low viability for all treatment groups (Table 1).

Table 1. Effect of immunotherapy.

Experimental groups	Number of pigs	Total cysts/kg	% of Cysticerci which failed to evaginate			
			Muscle	Tongue	Brain	All cysts
Membrane enriched antigen (MA)	5	245 (164)	15 (14)	13 (15)	48 (37)	17 (16)
Saline	7	524 (865)	7 (6)	5 (21)	41 (39)	16 (19)
Aqueous adjuvant antigens (AA)	9	283 (234)	28 (29)	46 (36)	48 (41)	34 (28)
Adjuvant	7	292 (261)	7 (6)	3 (11)	53 (40)	19 (15)
Immunotherapy (MA, AA)	14	272 (235)	23 (25)	39 (34)	46 (38)	28 (24)
Controls (saline, adjuvant)	14	408 (558)	7 (6)	11 (16)	47 (38)	14 (15)

These values are statistically different from each other $p<0.04$

The percentage of cysts that failed to evaginate and presumably not infective was calculated for each pig. The mean (SD) of these percentages for each treatment group are shown together with the total number of cysticerci identified per kg of tissue.

The large variation in the number of cysticerci found in the pigs in each treatment group (from 34 to 2,413 cysts/kg) led us to base the statistical analysis on the percentage viability of cysts for each tissue from each pig. This avoided potential bias introduced by the small number of heavily infected pigs and by the amount of each tissue dissected. Moreover, we repeated the above analyses using the total number of viable and non-viable cysticerci dissected from pigs in each treatment group and the pattern of significance was unchanged: overall, 35% of cysts dissected from pigs given immunotherapy were non-viable, compared with 10% of those from all of the control animals ($p<0.05$). In spite of these effects, at least a quarter of cysticerci were viable in every pig and more than half were viable in 11 of the 14 pigs given immunotherapy.

DISCUSSION

This blinded, randomized, controlled study confirmed that administration of cysticercal antigens to pigs naturally infected with *T. solium* cysticercosis caused a significant reduction in the viability of cysticerci for causing human tapeworm infection. The percentage of non-viable cysticerci was increased three-fold in pigs given AA in adjuvant and most of these animals developed new antibody bands detected by EITB.

In a previous study of immunotherapy, two cysticercotic pigs inoculated with MA developed eosinophilia and necropsy four and eight weeks later revealed histological findings suggestive of cyst degeneration.[16] However, the viability of cysticerci was not assessed in this study and the histopathological findings may have been biased by the small number of pigs and cysticerci studied, particularly in view of the highly variable inflammation we observed after administering the same dose of MA.

In a field trial in Mexico,[17] 1,076 doses of MA that was almost identical to the preparation we used were administered repeatedly to 447 pigs, although it was not clear how many doses each pig received. The prevalence of cysticercosis, as assessed by tongue palpation, fell significantly in the villages studied, but there was no control group, limiting interpretation of these results. Furthermore, their reliance on tongue palpation alone to assess response to immunotherapy may have been misleading since we found the effect of immunotherapy to be greater in tongue than other tissues. In this Mexican field trial, seven cysticercotic pigs given immunotherapy were studied in more detail and 73% of cysts excised from treated pigs failed to evaginate compared with 5% in seven untreated cysticercotic pigs. The ineffectiveness of MA in our study contrasts with these results and might be explained by the smaller number of vaccinations given, which may have induced a weaker immune response.

The partial effectiveness of AA immunotherapy and the variable inflammatory changes seen in adjacent cysticerci in our study would both be explained if the cysticerci infecting the pigs differed antigenically from the cysticerci used to prepare the immunotherapy. Morphological heterogeneity[21] and antigenic diversity[20] between cysticerci dissected from different naturally

infected pigs have both been noted and DNA probes have revealed genetic variation between different geographic isolates of porcine cysticerci.[27] However, our antigens were prepared from cysticerci obtained from pigs of the same area as those receiving immunotherapy, so antigenic heterogeneity is unlikely to be relevant.

At necropsy, control pigs that had been treated with saline had more cysticerci/kg tissue than pigs from the other groups. This is most likely due to random variations rather than treatment effects, because the differences did not approach statistical significance and there were no scars or calcifications present in the tissues of pigs given immunotherapy. In contrast, 12 weeks after drug therapy for porcine cysticercosis, calcifications were clearly visible at the site of degenerated cysticerci in previously infected meat[10] so it is unlikely that immunotherapy caused the disappearance of cysticerci without a trace in the same period.

The statistically significant effect of immunotherapy on *T. solium* viability illustrates the dynamic nature of the host-parasite interaction and the potential for manipulating this relationship to control parasitic infection. Genetically engineered, recombinant vaccines cause greater immunity against other tapeworm species[5,28] and identification and synthesis of the appropriate antigens for porcine cysticercosis may allow more effective immunotherapy. However, despite the statistically significant effect of immunotherapy on cysticercal viability in our study, all of the pigs remained macroscopically heavily infected with predominantly viable cysticerci. Immunotherapy alone is therefore unlikely to prevent human taeniasis.

SUMMARY

Taenia solium cysticercosis is an important cause of human disease in most developing countries. Porcine cysticercosis completes the parasitic life cycle and impairs meat production. A treatment for porcine cysticercosis may be an effective way of preventing human disease and would benefit pig farmers, facilitating control programs in endemic regions. Previous research suggests that re-infection with cysticercosis or immunotherapy with cysticercal antigens may cause degeneration of cysticerci, potentially curing porcine cysticercosis. We therefore performed a blinded, randomized, placebo-controlled study to assess the efficacy and safety of immunotherapy in 28 naturally parasitized pigs. Four groups of pigs with similar weight were inoculated twice with membrane enriched cysticercal antigens (MA), saline, aqueous-soluble crude cysticercal antigens (AA) in adjuvant (Freund's complete then incomplete), or adjuvant alone. Immunotherapy was well tolerated but had no consistent effect on the macroscopic appearance of cysticerci or eosinophil count.

Histopathological findings were variable with both severe and minimal inflammatory reactions seen in adjacent cysticerci in all pigs. Nine of 14 (64%) pigs given immunotherapy developed new antibody bands on electroimmunotransfer blot compared with one of 14 (7%) control pigs ($p<0.01$). Treatment with AA in adjuvant caused a significant increase in the proportion of cysticerci that failed to evaginate and were, therefore, not viable for infecting humans (34% for pigs given AA in adjuvant compared with 10% for adjuvant alone, $p<0.04$). Although immunotherapy caused a statistically significant fall in the viability of cysticerci, this immunological reaction was not great enough to prevent human disease.

RESUMEN

La cisticercosis por *Taenia solium* es una causa importante de morbilidad humana en muchos países en desarrollo. La cisticercosis porcina completa el ciclo de vida del parásito y afecta la producción de carne. Un tratamiento para la cisticercosis porcina podría representar una forma efectiva de prevenir enfermedad humana y beneficiaría a los criadores de cerdos, facilitando el desarrollo de programas de control en zonas endémicas. Trabajos previos han sugerido que la re-infección con cisticercosis o la inmunoterapia pueden causar degeneración de cisticercos establecidos, y potencialmente curar la cisticercosis porcina. En estas bases, realizamos un estudio randomizado, en ciego, controlado con placebo, para evaluar la eficacia y seguridad de la inmunoterapia en 28 cerdos naturalmente infectados. Cuatro grupos de cerdos de pesos similares fueron inoculados dos veces con antígenos enriquecidos de membrana de cisticerco (AM), salino, antígeno crudo de cisticerco en solución acuosa (AA) en adyuvante (adyuvante de Freund completo y luego incompleto), o adyuvante solo. La inmunoterapia fue bien tolerada, pero no tuvo efectos consistentes en la apariencia macroscópica de los cisticercos o en el número de eosinófilos.

Los hallazgos histopatológicos fueron variables, con reacciones inflamatorias severas o mínimas vistas en cisticercos adyacentes en cada cerdo. Nueve de 14 cerdos que recibieron inmunoterapia (64%) desarrollaron nuevas bandas de anticuerpos en la prueba de inmunoelectrotransferencia (EITB),

comparado con uno de los 14 (7%) cerdos en los grupos control (p<0.01). Tratamiento con AA en adyuvante causó un aumento significativo en la proporción de cisticercos que no evaginaron, y por lo tanto no eran ya viables para infección humana (34% en cerdos que recibieron AA en adyuvante comparado con 10% en los que recibieron solamente adyuvante, p<0.04). Aunque la inmunoterapia causó una disminución significativa de la viabilidad de los cisticercos, esta reacción inmunológica no fue de un grado suficiente para prevenir la infección en humanos.

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Sección II

Clínica y Terapéutica

Teniasis/Cisticercosis por T. solium

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