Meta-analysis. Cysticidal drugs for neurocysticercosis: albendazole and praziquantel

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CRD summary
The review assessed the effects of cysticidal drugs for neurocysticercosis. The authors concluded that cysticidal drugs result in better resolution of enhancing lesions and cysts, lower risk of recurrence of seizures in patients with enhancing lesions, and a reduction in the rate of generalised seizures in patients with cysts. This was a well-conducted review and the authors’ conclusions are likely to be reliable.

Authors’ objectives
To determine the effectiveness of cysticidal drugs on neuroimaging and clinical outcomes of patients with neurocysticercosis.

Searching
MEDLINE, the Cochrane Database of Systematic Reviews and LILACS were searched from January 1979 to August 2005; the search terms were provided. In addition, reference lists from cysticercosis books, key papers and relevant articles written by experts in cysticercosis were screened. No language restrictions were applied to the search.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion in the review.

Specific interventions included in the review
Studies in which at least one treatment arm received a cysticidal drug and another did not receive specific therapy were eligible for inclusion. The intervention, including cysticidal drugs and regimen used, was to have been consistent throughout each study group. All of the included studies used the cysticidal drug albendazole in at least one treatment arm; two studies used praziquantel. In some studies patients were given concomitant corticosteroids. The interventions were compared with placebo or no therapy.

Participants included in the review
Studies of participants with neurocysticercosis, in which the viability and location of parasites was described and homogeneous across study groups, were eligible for inclusion. Patients in the included studies had a single enhancing lesion, 2 to 3 enhancing lesions, a cystic lesion, or multiple cystic lesions. The majority of the patients had seizures.

Outcomes assessed in the review
Studies that provided the number of patients with complete resolution of lesions or the total number of intracranial lesions, based on neuroimaging, before and after therapy were included. Trials were not excluded for not having a specific clinical end point if the data allowed objective evaluation of the intervention on the basis of neuroimaging findings. Studies had to perform an imaging evaluation at predefined times after the intervention, and also provide the times of the evaluations, to be included in the review. The outcomes in the review were the numbers of active and persisting lesions, as determined by neuroimaging, and the percentage of patients with seizure recurrence.

How were decisions on the relevance of primary studies made?
Three authors independently reviewed the articles for inclusion. Any disagreements were resolved through discussion until consensus was reached.

Assessment of study quality
Study quality was assessed according to the operational variables suggested by the U.S. Preventive Services Task Force for internal validation of RCTs. Such variables included assessment of randomisation procedure, comparability of
groups, differential loss to follow-up, reliability of measures, definitions of intervention, whether important outcomes were considered, and use of an intention-to-treat analysis. Each study was given an overall quality rating of good, fair or poor. One author who had not previously been involved in trials of cysticidal drug therapy carried out the quality assessment.

Data extraction
Three authors independently extracted the data. Any disagreements were resolved through discussion and consensus. Data were extracted for the number of participants randomised, percentage of participants lost to follow-up, intervention, adverse events, timing of control neuroimaging studies, main outcomes and duration of follow-up. The data were grouped in stratified 2x2 tables.

Methods of synthesis
How were the studies combined?
The results of studies with participants with parenchymal brain-enhancing lesions and those of studies with participants with intracranial cystic lesions were combined as odds ratios (ORs) using the Mantel-Haenszel fixed-effect model, and 95% confidence intervals (CIs) were calculated.

How were differences between studies investigated?
Heterogeneity was assessed using the chi-squared test and the I-squared statistic. Where statistical heterogeneity was detected, a random-effects model was used. A subgroup analysis of studies in which corticosteroids were routinely given to one or more study groups was also performed.

Results of the review
Eleven RCTs (n=936), of which 5 were double-blind RCTs (n=368) and 6 were non-blinded randomised trials (n=568), were included in the review.

Five trials were rated as having good methodological quality, 1 was fair, 3 were fair or poor, and 2 were poor.

Neuroimaging outcome: enhancing lesions (5 studies).
Seventy-two per cent of patients treated with a cysticidal drug and 63% of untreated patients showed improvement on computed tomography (CT) scans. The chi-squared test for homogeneity was not statistically significant (P=0.19), but the I-squared statistic (34%) suggested marginal homogeneity. Using a random-effects model, there was no statistically significant difference between treatment groups for the number of participants without lesions (OR 1.18, 95% CI: 0.82, 1.71, P=0.38). When the one trial thought to be the cause of the heterogeneity was removed, the results were statistically significant in favour of the cysticidal drug (OR 1.93, 95% CI: 1.21, 3.08, P=0.006), and no significant statistical heterogeneity was detected.

Neuroimaging outcome: cystic lesions (6 studies).
Forty-four per cent of treated patients and 19% of untreated patients had complete resolution of all cystic lesions on CT scans or magnetic resonance imaging. The chi-squared test for homogeneity was not statistically significant (P=0.22), but the I-squared statistic (29%) suggested marginal homogeneity. When a random-effects model was used, there was a statistically significant difference between groups in favour of the treated group (OR 2.10, 95% CI: 1.10, 4.01, P=0.025).

Based on 5 studies, there was a greater reduction in the total number of cysts in treated patients than in untreated patients, but the difference was not statistically significant at the 5% level (random-effects OR 3.55, 95% CI: 0.81, 15.52, P=0.092). Removing one of the studies because it was thought to be the cause of statistical heterogeneity revealed a stronger relationship between a reduction in number of cysts and treatment with a cysticidal drug (OR 14.79, 95% CI: 10.16, 21.53, P<0.001), and no significant statistical heterogeneity was detected.

Seizure recurrence: enhancing lesions (4 studies).
There were statistically significantly fewer seizures during follow-up in the treated patients (14%) than in the untreated patients (32%) (OR 0.36, 95% CI: 0.21, 0.62, P<0.001). No significant statistical heterogeneity was detected (P=0.68, I-squared 0%).

Seizure recurrence: cystic lesions (2 studies).

One study, in which all patients had epilepsy, found that patients treated with albendazole showed a significant (67%) reduction in the rate of seizures involving loss of consciousness after the first month of treatment (P=0.003). In the other study, only some patients had epilepsy, and no information about the frequency or severity of recurrences in individual patients was provided.

Effects of corticosteroids on cysticidal drug efficacy.

One study found that albendazole plus a corticosteroid (dexamethasone) was no better than albendazole alone in terms of lesion resolution or risk of seizure recurrence during follow-up.

Safety of cysticidal drugs.

Adverse events related to treatment were poorly reported. Many patients reported mild headache, nausea, or abdominal discomfort. Some patients had a transient exacerbation of seizures during the trial, and a few developed signs of increased intracranial pressure. The occurrence of adverse events did not depend on the type of cysticidal drug used or whether patients were receiving corticosteroids.

Authors' conclusions

Treatment with cysticidal drugs results in better resolution of both enhancing lesions and cysts, as well as a lower risk of recurrence of seizures in patients with enhancing lesions and a reduction in the rate of generalised seizures in patients with cysts.

CRD commentary

The authors set out a clear objective at the beginning of the review. The inclusion criteria were defined clearly in terms of the participants, interventions, outcomes and study design. Relevant sources were searched and no language restrictions were applied, which helps to reduce the risk of language bias. However, the authors appear to have made no attempts to search for unpublished data and this increases the risk of publication bias. The study selection and data extraction processes were carried out by three independent reviewers, which helps to reduce the risk of errors and bias. The quality of the included studies was assessed on appropriate criteria; however, only one reviewer carried out the assessment, thus increasing the risk of errors.

Appropriate study details were provided for each of the included studies. Combining the studies in meta-analyses appears appropriate. This was generally a well-conducted review and the authors’ conclusions are likely to be reliable. It should be noted, however, that the conclusion regarding the effects of cysticidal drugs on generalised seizures in patients with cysts was based on the results of just one study, albeit one of good quality.

Implications of the review for practice and research

Practice: The authors stated that the results did not suggest an optimal therapeutic regimen for neurocysticercosis. The evidence favours albendazole over praziquantel, and larger courses of albendazole may be needed for patients with several cystic lesions. Further research is needed.

Research: The authors stated that the role of corticosteroids as an adjunctive treatment in the routine management of patients with neurocysticercosis who have mild infections has yet to be determined. They stated that future trials should not compare cysticidal drugs with placebo or no therapy, but rather compare different regimens of cysticidal drugs in order to determine the optimal therapeutic agent.
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