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Antiparasitic drugs in neurocysticercosis: albendazole or praziquantel?

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SUMMARY

This article evaluates the findings and conclusions of a recent meta-analysis of published data comparing the efficacy of the treatment of neurocysticercosis with albendazole and praziquantel in terms of both resolution of brain cysts and seizure control. From 103 related articles indexed in PubMed and the Cochrane Database of Controlled Trials, and quoted in reference lists, six prospective trials comparing albendazole with praziquantel (including patients infected with parasites in their cystic stage without perilesional inflammation and examining partial or total disappearance of cysts and/or control of seizures) were evaluated. The small number and heterogeneity of the included studies makes it difficult to assess the analyses provided. One of the studies was a pilot trial, at least three had grossly inadequate sample sizes and, owing to the way in which the data are presented in one of the studies, it is not possible to extract the proportion of parasites that resolved. None of the studies was designed to evaluate seizure control. The current published data does not provide enough basis to determine conclusively the superiority of either albendazole or praziquantel as first-line treatment of neurocysticercosis, and the choice of an antiparasitic drug is still guided by collateral factors, including drug availability and costs.

The larvae of *Taenia solium* frequently locate in the human CNS, causing neurocysticercosis (NCC). NCC continues to be a frequent cause of seizures and epilepsy in many countries, with increasing numbers of cases diagnosed in nonendemic countries, owing to immigration from and travel to endemic regions [1]. The clinical manifestations of NCC vary according to several factors, including the location, size, number and evolutive stage of the parasites, and the immune response of the host. Intraparenchymal brain cysticercosis presents with seizures as its major manifestation, while extraparenchymal (subarachnoid and ventricular) cysticercosis is associated with intracranial hypertension and hydrocephalus [2,3].

Viable brain cysts eventually degenerate, provoking a host inflammatory response, and later evolve into granulomas that frequently calcify. The use of antiparasitic drugs, either albendazole (ABZ) or praziquantel (PZQ), accelerates this process, apparently by exposing parasite antigens to the action of the host's cellular immune response. Antiparasitic therapy leads to cyst degeneration, with acute inflammation followed by cyst death within a few weeks. Most intraparenchymal cysts leave a residual, calcified scar. Despite a long debate over whether cyst destruction through the use of antiparasitic agents is of benefit to the evolution of the underlying seizure disorder, by now, most authors include them as part of the management of most types of viable or degenerating cysts.

The use of PZQ for NCC was first reported in 1979 [3–5], for 15 days at 50 mg/kg daily. Neurological side effects related to brain inflammation (in turn, related to cyst degeneration) were reported soon after, and included some instances of death [6]. Steroids were added to decrease inflammation and intracranial hypertension. However, pharmacokinetic studies showed that PZQ concentrations decreased when administered with steroids [7]. A Mexican group reported the use of a single-day scheme of three doses of PZQ 25 mg/kg at 2-h intervals, delaying the administration of steroids until the peak concentrations of PZQ had been sustained [8]. For unknown reasons, the efficacy of this single-day scheme seems better in patients with a single lesion than in those with more parasite cysts [9,10]. ABZ was first reported for treating NCC in 1987 [11], initially administered for 1 month at 15 mg/kg daily. Later studies suggested that the efficacy was similar when administered over 15 days, or even over 7 days [12–14].

METHODS

Studies indexed under ‘albendazole’, ‘praziquantel’, ‘neurocysticercosis’ or ‘*Taenia solium*’ in PubMed and the Cochrane Database of Controlled Trials, or quoted in reference lists, were assessed by two independent reviewers and disagreements were resolved by consensus [15]. The authors selected prospective trials comparing ABZ with PZQ for the treatment of patients with NCC. Trials needed to include patients infected with parasites in their cystic stage without perilesional inflammation and to examine partial or total disappearance of cysts and/or control of seizures. Quality of included trials was analyzed by using the Jadad score.

The meta-analysis had, as its primary outcome, the proportion of patients with controlled seizures. Secondary outcomes included a reduction in the numbers of cysts, proportion of patients with total disappearance of cysts, proportion of patients with adverse events related to the study drugs and proportion of patients with intracranial hypertension secondary to antiparasitic treatment.

RESULTS

From 103 potentially responsive articles, 91 were excluded because they did not examine the comparison between PZQ and ABZ. Of the remaining 12 papers, six studies did not meet the specific inclusion criteria set for the meta-analysis. In the end, only six trials were included in the meta-analysis; of note, only two were randomized, controlled trials.

Examined studies differed in doses and duration of therapy for ABZ and PZQ. According to the data, most of the studies administered 15 mg/kg daily of body weight of ABZ and in only one study, ABZ was administered at a dosage of 20 mg/kg daily. The duration of therapy varied from 8 days to 1 month. The duration of PZQ therapy extended from a single day to 3 weeks. In all of the studies, the dosage of PZQ was 50 mg/kg daily, except one study in which PZQ was administered at a dosage of 100 mg/kg for a single day. PZQ data was pooled on the assumption that the administration of PZQ for a single day is as effective as for longer periods of therapy.

A total of four out of the six studies are quoted as reporting data on the complete control of seizures in patients treated with ABZ or PZQ. The percentage of control of seizures ranged from 63.5 to 100% with ABZ treatment, and from 41.7 to 77.8% with PZQ treatment. ABZ was associated with better control of seizures in comparison with PZQ in the pooled data analysis.

In five out of six studies, data reported that there was a significant reduction in the total number of cysts from baseline to follow-up. The percentage reduction of the total number of cysts ranged from 41.2 to 89.8% with ABZ and from 41.5 to 79.2% with PZQ. A total of 301 patients with 2565 cysts were included in the analysis. There was no statistically significant difference in the proportion of the reduction of cysts between both treatments.

All six studies reported data on the total disappearance of cysts. The proportion of patients with total disappearance of viable cysts ranged from 28.1 to 80% with ABZ and from 15 to 79.2% with PZQ. When all studies were included in the analysis, ABZ was significantly more related to total cyst disappearance.

From all six studies, only one death was reported, which was due to increased intracranial pressure. Adverse events and secondary intracranial hypertension events were reported in five out of the six studies. In four out of the six studies, ABZ and PZQ did not differ in the proportion of patients with adverse events or intracranial hypertension.

DISCUSSION AND SIGNIFICANCE

Neurocysticercosis is a very complex disease, with multiple variables strongly affecting its clinical manifestations and response to treatment. These variables include the number, size, stage and location of the parasites in the nervous system, and the immune response of the host [16]. Antiparasitic treatment is designed to kill living cysts and contribute to better seizure control [17], which, in turn, is closely related to and strongly dependent upon appropriate concomitant antiepileptic drug therapy.

An overall assessment of the literature suggests approximately 65–75% of parasites die after an initial course of antiparasitic treatment, with total cure rates of approximately 35–40%. From this large body of uncontrolled data, ABZ seems to have a somewhat higher cysticidal efficacy than PZQ. A usual question for the attending neurologist in most developing countries is whether to choose ABZ or PZQ as the first option for antiparasitic treatment of viable NCC. Other factors affecting this decision are drug availability (ABZ is far more available than PZQ, which is not commercially available in many countries), cost (in general, ABZ is cheaper than PZQ, albeit generic versions may overcome this issue) and side effects (transient increases in liver enzymes and, more rarely, decreases in blood cell counts can occur under ABZ treatment).

The authors made a bona fide effort to answer the above question. Unfortunately, the small number and heterogeneity of the included studies does not allow a conclusive definition of superiority. One of the studies was a pilot trial, at least three had grossly inadequate sample sizes and, from the way the data are presented in one of the selected studies, it is not even

possible to extract the proportion of parasites that resolved. None of the studies were designed to evaluate seizure control.

Probably, paraphrasing the authors (originally written in relation to post-treatment mortality data), 'the selected/examined data were not adequate to allow a meaningful analysis'. The authors are, however, right in highlighting the need for controlled studies comparing ABZ with PZQ. Adequately controlled testing of other potential drugs (i.e., oxfendazole) and drug combinations (i.e., ABZ plus PZQ) should be added to this list.

EXPERT COMMENTARY

To assess data on post-treatment response in NCC is not an easy task. By being an overlooked, neglected disease (not even included in the list of neglected diseases published by the WHO), funding is scarce and attention is minimal. This results in mostly uncontrolled literature and many small trials with insufficient sample sizes. A meta-analysis seems a reasonable option to make more sense of this scattered information. However, meta-analyses depend on the quality of individual studies, as well as on the homogeneity of their study designs and evaluated outcomes. This is not the case in the reviewed paper, and the few selected studies differ widely in doses, duration of treatment, type of patients (some included patients with intracranial hypertension as the predominant manifestation) and other key variables. Most of these studies were not even designed or sized to evaluate seizure control.

A major issue when examining the literature in NCC is the lack of comparability between studies. Up until the 1990s, the majority of authors included patients with intra- and extraparenchymal NCC together in studies evaluating diagnostic and therapeutic agents for this disease. It is clear now that NCC should be studied in better defined patient subgroups to allow sound interpretation (external validity) of published results.

The best contribution of this manuscript would probably be to focus the attention on the need for well-designed, controlled studies comparing diverse antiparasitic drug treatment schemes in NCC.

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KEY ISSUES

*Neurocysticercosis is a major cause of neurological morbidity in most developing countries.

*Intraparenchymal brain parasite larvae are predominantly associated with seizures and epilepsy, while extraparenchymal parasites commonly present intracranial hypertension as the major manifestation.

*Treatment of live parasites with antiparasitic agents results in parasite resolution. In the case of intraparenchymal cysts, parasite death apparently results in better control of seizures.

*Many case series and uncontrolled studies have been published using diverse regimens of praziquantel and albendazole.

*To date, there is minimal adequately controlled evidence that has been published, and it does not allow to conclusively determine the antiparasitic drug of choice based on antiparasitic efficacy.