Original Article

Safety and efficacy of clobazam versus phenytoin-sodium in the antiepileptic drug treatment of solitary cysticercus granulomas

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Background: It is now agreed that the prognosis of seizure disorder due to solitary cysticercus granuloma (SCG) is generally good. However, the choice antiepileptic drugs (AEDs) remain empirical, with no comparative trials of different AEDs being available. Aims: To determine the safety and efficacy (measured by the incidence of ‘treatment failure’) of clobazam in comparison to standard treatment with phenytoin-sodium for prevention of seizures in persons with solitary cysticercus granulomas (SCGs).

Settings and Design: This pilot study was conducted in a neurology department of a medical college hospital in the form of a prospective, randomized, open-labeled trial.

Materials and Methods: Forty-eight patients with seizures due to SCG were randomized in an open-labeled trial to either, clobazam (1 mg/kg oral loading followed by 0.5 mg/kg/d) (n=21) or phenytoin (15 mg/kg, oral loading in 3 divided doses over 24 h, followed by 5 mg/kg/d) (n=27). They were followed over 6 months with the primary outcome measure being treatment failure (either discontinuation or modification of AEDs) due to either adverse effects or breakthrough seizures.

Results: Treatment failures were noted to be significantly less common (P=0.03) in the clobazam-treated group (n=1; 4.7%) than in phenytoin-treated group (n=9; 33.3%). These included one patient (4.7%) in the clobazam-group who had breakthrough seizures and 3 (11.1%) who had breakthrough seizures and 6 (22.2%) in the phenytoin-treated group who had adverse effects requiring treatment discontinuation.

Conclusions: Clobazam was well tolerated, safe and more effective than phenytoin in the AED treatment of patients with SCG.

Key words: Neurocysticercosis, seizures, antiepileptic drugs, clobazam, phenytoin

Introduction

Single enhancing lesions (SELs) are commonly noted upon imaging studies of young persons with new-onset seizures in several neurocysticercosis-endemic geographic regions.[1-3] The lesions are believed to represent involuting solitary cysticercus granulomas (SCGs).[4] Treatment policies vary between administration of antiepileptic drugs (AEDs) alone or in combination with a course of anthelminthic agents.[5,6] Phenytoin-sodium and carbamazepine are the commonly used AEDs for seizure control in such situations.[7] There is no published experience with other AEDs. We and other authors have reported the occurrence of cutaneous adverse reactions including anticonvulsant hypersensitivity syndrome (AHS) among individuals with SCG being treated with phenytoin and carbamazepine.[8-10]

Clobazam, one of the AEDs has been used in a variety of seizure disorders.[11-13] It has the advantages of a rapid onset of action[13] and minimal side effects,[11] in particular allergic cutaneous reactions.[11] In this communication, we report our preliminary experience with this agent in a prospective, randomized, open-label comparison with phenytoin-sodium. We sought to determine whether clobazam was well tolerated, safe and efficacious in the AED treatment of SCGs.

Materials and Methods

Study population

The study commenced after Institutional Review Board approval on March 18th, 2002 through May 29th, 2003. Trial participants were recruited from the Outpatient Neurology Clinic of Dayanand Medical College, Ludhiana, Punjab. All those above 12 years of age, with recent (< 2 weeks) generalized seizures or focal seizures with or without secondary generalization, who were...
not already on AED treatment, in whom imaging demonstrated a SCG defined according to previously established criteria were included. Patients with a concomitant serious systemic disorder, pregnant women and those unwilling to comply with follow-up schedules and those presenting in status epilepticus or with seizure clusters (defined as 2 or more seizures in 24 hours prior to presentation) were excluded from the study.

**Materials and Methods**

At inception, the study planned to enroll 135 subjects to each of the 2 groups mentioned below, in order to provide sufficient power to detect 10% difference in the primary outcome measure with 90% confidence. The numbers accrued, however fell short on account of premature termination of the study due to relocation of one of the study team members.

Participants were randomized strictly according to a computer-generated random list, available with the recruiting physician to receive either phenytoin-sodium (Magnus, India) in a loading dose of 15 mg/kg orally, divided in to 3 doses administered over one day followed by 5 mg/kg/day rounded to the nearest 50 mg dose or clobazam in a dose of 1 mg/kg oral loading followed by 0.5 mg/kg/day for at least six months. Each participant collected the medication from an appointed person who dispensed medicines after accounting for the previous supply issued. None of the patients received any cysticidal treatment.

Patients were followed-up at 1, 2, 3 and 6 months at which time medications were dispensed according to their randomization number. They were allowed unscheduled visits if required. Complete blood count, serum chemistries including serum urea, glucose, liver transaminases, alkaline phosphatase and creatine kinase were done upon entry to trial and at one and three months. Serum levels of phenytoin were not routinely monitored in view of cost and restricted availability. Plain and contrast enhanced brain CT were done on all participants who completed the study at six months. CT findings were classified as “complete resolution”, “partial resolution”, “resolution with calcification”, “persistent lesion” in order to guide further AED treatment. AEDs were tapered off over one month in patients who completed the trial if CT revealed complete resolution of the SCG. In event of an alternative CT outcome, treatment was continued. AEDs for the post-study phase were also provided free of charge. In addition to the treating physician, an independent research team member evaluated seizure control and adverse events at follow-up. He was blinded to treatment arms for the duration of study. All data was stored with him. He recorded the occurrence of breakthrough seizures and adverse events as reported spontaneously by the participants and following this, tallied the latter to an inventory of AED-adverse effects published previously elsewhere. The importance of compliance was explained and reinforced at each visit. Antiepileptic drug levels were not done in view of cost.

**Outcome criterion**

Participants who developed breakthrough seizures or adverse effects that required discontinuation or modification (with increased dose or with additional AED) of treatment schedule were labeled as ‘treatment failures’. The total number of treatment failures in each group due to breakthrough seizures or adverse events during the first six months of follow-up constituted the primary outcome measure in this study. Patients who exited the study prematurely on account of the above reasons were given an escape treatment that comprised of either increased dosage of the same AED or an alternative AED.
**Statistical evaluation**

Analysis was done on an “intention to treat” principle. The numbers of participants exiting the study due to either breakthrough seizures or adverse events in the two groups were compared using the Fisher’s exact test. \( P\leq0.05 \) were considered significant.

**Results**

The trial enrolled 48 patients including 27 [17 (63.0%) males and ten (37%) females; mean age: 28 ± 12 years; range: 12-66 years, 95% CI: 23-32] who received phenytoin sodium and 21 [14 (66.7%) males and 7 (33.3%) females; mean age: 18 ± 9 years; range: 12-46 years, 95% CI: 14-22] who received clobazam. There were no statistically significant differences in the mean age and gender distribution of the phenytoin-treated and clobazam-treated groups.

There were 9 (33.3%) treatment failures in the phenytoin-treated group in comparison to one (4.7%) treatment failure in the clobazam group. When analysed on an intention to treat basis, this difference was statistically significant (\( P=0.03 \)). Throughout the study period, at least 22 (81.5%) patients in the phenytoin-treated group and at least 19 (90.3%) patients in the clobazam-treated group remained seizure free.

In the phenytoin-treated group, three (11.1%) patients had breakthrough seizures in the follow-up study period. Clobazam was added to the treatment regimen in these patients. Six (22.2%) patients were discontinued from medication prior to completing the study on account of adverse effects. This included five (18.5%) patients who developed either an allergic skin rash (\( n=4 \)) or frank anticonvulsant hypersensitivity syndrome (\( n=1 \)) at 11–28 days after initiation of treatment. One (3.7%) patient was discontinued from phenytoin after four months after treatment initiation due to severe gum hypertrophy. Another patient developed hepatitis (due to hepatitis A virus) that resolved spontaneously whilst on treatment; phenytoin doses were managed accordingly to serum levels during this period. Thus, nine (33.3%) patients failed treatment either due to adverse effects or breakthrough seizures in the phenytoin group.

In the clobazam-treated group, one patient (4.7%) developed breakthrough seizures at four months after initiation of treatment; phenytoin was added to his treatment regimen. No patients required treatment discontinuation due to adverse effects. One (4.7%) patient had a transient skin rash that resolved within one week without treatment discontinuation. Incidentally, clobazam caused intolerable sedation requiring discontinuation in one subject who was given the medication as an escape treatment following phenytoin-induced skin rash.

Two (7.4%) patients in the phenytoin-treated group were lost upon first follow-up visit. Telephonic inquiries revealed that the family of one had relocated and could not be traced subsequently, whilst the other committed suicide three weeks after treatment initiation. The circumstances that led to suicide were reported to be “loss of mental balance due to financial reasons”. There was no indication from the telephonic interview or from review of patient’s notes whether the subject suffered from current or prior depression. The case was reported to the Institutional Review Board. An internal review committee constituted by the study team members took the view that the suicide was not related to phenytoin administration. One patient in the clobazam treated group violated the protocol by electing to take a different AED upon the advice of another physician.

The profile of adverse effects of the two AEDs is shown in Table 1. In the clobazam-treated group, 14 subjects (66.7%) reported an adverse event, whilst the number reporting an adverse event in the phenytoin group was 19 (70.4%). Mild sedation was commonly reported by subjects in both groups. Whilst generalized weakness, skin rash and gum hypertrophy were reported in the phenytoin-treated group, weight gain and mild headaches were common side effects in the clobazam-treated group.

**Discussion**

This study demonstrated the superiority of clobazam over phenytoin when treatment discontinuation or modification (labeled as treatment failure) due to either adverse events or breakthrough seizures was used as an outcome measure. The major limitation of the study was its small sample size, which precluded ascertainment of the true magnitude of the effect studied and also evaluation of differences in measures of efficacy and safety, separately. Nevertheless, the size of this study had sufficient power to detect a 30% difference in the primary outcome with 90% confidence.

The AED treatment policies for SCGs remain unclear and guided by intuition rather than firm scientific basis. There are no clear guidelines for the specific AED to be used. A rapid onset of action is desirable, in view of that seizures are often clustered and accordingly there would a high risk of seizure recurrence at the time of administration of a seizure.\(^{(15)}\) Clobazam appears to be suitable to the AED treatment of SCGs in view of its rapid onset of action. Clinical experience shows it to be efficacious in the prophylaxis of acute symptomatic seizures and febrile seizures.\(^{(11-13)}\) The dose of clobazam used by us was based upon recommendations for its use in the prophylaxis of acute febrile seizures.\(^{(15)}\) The proportion of subjects reporting adverse reactions with clobazam in such doses compared favourably with proportion of subjects who reported adverse effects with phenytoin.

Phenytoin-sodium is perhaps most frequently used in the management of seizures due to SCG because of its rapid onset of action following loading dosage. However, it has been found to be associated with a high risk of allergic skin phenomena including anticonvulsant hypersensitivity syndrome.\(^{(14-16)}\) Under such circumstances, carbamazepine would also be unsuitable due to known cross-reactivity between the two agents in their propensity to cause hypersensitivity phenomena. Clobazam appears to be a useful alternative, in as much as it does not cause cutaneous
adverse reactions.[13]

The reader is cautioned against making any conclusions about the efficacy of phenytoin vis-à-vis clonazepam, since blood levels were not estimated in event of breakthrough seizures; hence it could be possible that breakthrough seizures in the phenytoin-treated group were on account of sub-therapeutic levels of the agent.

It may be worth adding that phenytoin-sodium induces the metabolism of anthelmintic agents, thereby reducing their serum levels and potentially compromising their efficacy.[14] Similar drug interactions have not been demonstrated for clonazepam, though it would be pertinent to study the nature of interactions, if any between the drug and anthelmintic agents.

Phenytoin remains a primary option for seizure management, particularly in resource-limited countries, being widely available and inexpensive. According to calculations based on drug prices in India, a six-month course of phenytoin administered to a 70 kg adult would cost Rs. 8,050. In comparison, the cost of a six-month course of clonazepam would be Rs. 39,600. However, one has to add to the cost of phenytoin treatment, hidden and overt expenditure incurred on treatment of adverse drug reactions including hospitalization and days spent off work.

**Conclusion**

This pilot, randomised, open labeled trial demonstrates the safety, tolerability and efficacy of clonazepam in the AED treatment of SCGs. However, larger prospective comparisons that are blinded are required to make definite conclusions about its use in the management of acute symptomatic seizures not only due to SCGs and other conditions such as meningitis and encephalitis.

**References**