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Use of Lamotrigine in Uncontrolled Epileptic Patients at a Paediatric Neurology Clinic in Pakistan

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SUMMARY

Despite the availability of a large number of antiepileptic drugs a significant number of epileptic patients remain without adequate control or suffer from significant side effects of the drugs. Out of a total of 241 epilepsy patients being followed at the paediatric neurology clinic 16 such resistant epileptic patients between the ages of 3 months to 13 years were identified. All of these patients had their basic laboratory testing and EEG. Thirteen had CT Scans of their head. Two of these patients had a history of birth hypoxia, three had microcephaly with developmental delay and four were postmeningitic. Clinically progressive myoclonic epilepsy was seen in another four patients, there being a single patient each having infantile spasms and a neurocutaneous syndrome. Eleven patients had generalised seizures and five patients and focal epilepsy. All patients were already taking multiple antiepileptic drugs such as Phenobarbitone, Clobazam, clonazepam, diazepam, valproic acid and Carbamazepine. All of these patients were put on Lamotrigine in a dose of 2.5 to 7.5 mg/kg per day in two divided doses given orally. The previous medication used was gradually withdrawn. These patients were followed up every month and the effects, side effects clinical response and development was monitored. They were followed by us for a varying period of three to twelve months and the results were analysed. Fourteen patients needed a combination of Lamotrigine with another anti epileptic drug whereas in two Lamotrigine monotherapy was enough. All patients showed clinical improvement with decrease in seizure frequency as well as improvement in cognition and behaviour. One patient required decrease in dose due to appetite loss and rash. All other patients tolerated the medication well.

INTRODUCTION

About 50 million patients suffer from epilepsy with 5 million having uncontrolled seizures. Over the centuries a number of substances have been tried to control seizures. Bromides were the first drugs available until the arrival of Phenobarbitone in 1912. Sedation remained a major problem till the introduction of Phenytoin in 1938. Carbazamepine and Valproate became available in the 1970s. A number of advisory boards are working including the epilepsy branch of the National Institute of Neurological Disorders to advance the field of epilepsy treatment. In 1969 an antiepileptic development programme was initiated. This has resulted in the production of several drugs that may be used in paediatric epilepsy including Lamotrigine. Recommendations have been made for clinical trials in children[1]. Almost all new antiepileptic drugs are intended for all age groups. A number of international experiences are available in the use of Lamotrigine in the paediatric age group especially in resistant epilepsies[2].

PATIENTS AND METHODS

Out of the 241 patients with epilepsy being followed at the paediatric neurology clinic 16 resistant epileptic patients ranging in ages from 3 months to 13 years were identified.

All patients were already on multiple medications with various combinations of antiepileptic drugs. Despite polypharmacy there was inadequate control of their seizures. Initially the drug combinations were rationalised and dosage increased to the maximum tolerated range. Only those patients who failed to have control of their seizures despite a three month follow up were included in the study. Hence only carefully selected patients with resistant epilepsy whose families were desperate to seek alternative therapy were included in the study for initial experience. All of these patients had their basic laboratory testing and EEG and 13 also had CT Scans of the Head. Once on treatment follow up was performed on a monthly basis. Blood biochemistry and Haematological parameters along with Liver Function Tests were performed at the start of therapy and six months, tests being done in the intervening period only if necessary for example if the patient developed a rash. Daily seizure count and seizure calendar are maintained by the family and reviewed at each clinic visit.

RESULTS

Age Distribution was 0-1 year 4 patients, 1-5 years 8 patients 5-10 years 2 patients and 10-15 years 2 patients. 11 were male patients and 5 were females. Two of these patients had a history of birth hypoxia, three with microcephaly and developmental delay and four had postmeningitic brain damage. Clinically progressive myoclonic epilepsy was seen in another four patients, there being a single patient each with a neurocutaneous syndrome and infantile spasms. Eleven patients had generalised epilepsy and five had focal seizures as defined by the International League against Epilepsy Classification[3]. All patients were already taking multiple anti epileptic medications.

Four patients were found to have focal epileptic discharges (spikes) on their EEG records. Generalised spike and waves were seen in six patients, multifocal discharge in three patients, nonspecific slow waves in were seen in one patient and hypsarrythmia in one patient. One patient has a normal interictal EEG.

Fourteen of the patients had neuroimaging. CT Scans of the head were performed on thirteen patients. Two Scans was normal. Findings were seen in the other patients. Six of the patients had atrophic changes in the brain. One had a chronic post infective subdural effusion while two had hydrocephalus on CT Scan one of these patients needing ventriculoperitoneal shunt insertion. One patient also had an MR Scan of the Brain showing atrophy and post infective demyelination. Cranial ultrasound was reported normal in one patient.

The duration of treatment is between three to ten months. Two patients have shown significant response and have been converted to monotherapy. Eight patients have shown reduction in seizure frequency of at least 50%. Six patients have shown an inadequate response at the present dose and are on an accelerated dosage regimen. Dosage used so far is 2.5 mg/kg/day to 7.5 mg/kg/day. The lower dose is used with Valproic Acid. One patient on both these drugs has needed dosage reduction due to a rash and has no side effects on 2 mg/kg/day. However he has breakthrough generalised seizures at least once a week with an interictal EEG showing a slow background and anterior dominant spike and wave. Most parents have noted a better cognition, behaviour and increased alertness which is probably due to better seizure control and the discontinuation of the more sedative drugs as a result of the beneficial role of Lamotrigine.

DISCUSSION

Lamotrigine is a compound developed during a search for substances possessing an antifolate activity being unrelated to any other conventional anticonvulsant in use today. Subsequent studies have demonstrated that its anticonvulsant effect is unrelated to antifolate activity. It has been proposed that the mechanism of action is to block the voltage sensitive sodium channels in the cell membrane with the inhibition of release of excitatory amino acid glutamate from nerve terminals[1]. A summary of the pharmacokinetic data is given in Table 1. Spectrum of activity of epilepsy is similar to that of Phenytoin and Carbamazepine in animal models[5]. In some models it appears to have a broader spectrum and better tolerability than the above agents. In clinical trials as add on therapy in medically refractory partial seizure patients Lamotrigine produces 50% seizure frequency reduction in 25-30% patients. Lamotrigine is well tolerated even in add on situations which appears to be related to positive behavioural effects. The most significant adverse effect is rash which has led to withdrawal of the drug in 2% of exposed patients in clinical trials.

Table 1:

Lamotrigine characteristics.
- Rapid oral absorption
- Time to peak serum level 2-3 hours
- Protein bound 55 %
- Monotherapy elimination half life 15-50 hrs
- Concurrent enzyme inducers 8 - 33 hrs
- Concurrent enzyme inhibitors 30 - 90 hrs
- Elimination metabolic

Drug interactions
- Half life significantly affected by concurrent drug administration
- Liver enzyme induction none
- Adverse effects neurotoxicity.
- Rash requiring decreased drug dosage is common

Concomitant drug administration requires diligence as a number of drugs affect its administration. It appears to be well tolerated except for the rash which is more common when Lamotrigine is combined with Valproic Acid[6]. It is clearly effective in reduction of seizure frequency and in this clinical setting the response although useful is usually not dramatic. Our findings of ten out of sixteen patients having achieved at least 50 % seizure frequency reduction with that in the literature. Similarly the rash as seen in one patient requiring medication reduction has been previously reported. Despite the fact that most previous studies were undertaken on focal seizures our study included eleven patients with generalised epilepsy as previously patients with resistant childhood epilepsies and with Lennox Gastaut Syndrome have shown positive results[7,8,9]. The possibility of efficacy in absence and other generalised epilepsies is suggested by the observation that Lamotrigine can suppress photoconvulsive responses as well as the frequency of spike and wave discharges[10]. Our experience with Lamotrigine in Paediatric epilepsy is that it is a broad spectrum antiepileptic agent and should be also used in generalised seizures. This has also been seen in open labelled studies in a variety of treatment resistant childhood seizure disorders.

Lamotrigine has generally been tried only in refractory seizures[9] and as adjunctive therapy[11,12]. Results are now available of trials with Lamotrigine as an initial drug in the treatment of epilepsy[13]. We need to gain further experience in our own local clinical setting as the requirements may be different due to local cultural and economic factors.

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