Editorial

RESISTANT SEIZURES

CHILDHOOD epilepsies may be self limiting, stop within several years and generally respond to medical therapy (l). Some epileptic syndromes, neuro-anatomic anomalies, neurometabolic and neurodegenerative processes are exceptions (2). These resistant seizures pose a serious problem for the treating physician, the patient and his family. There is no unanimity in the definition of 'resistant seizures' but they may be described as *seizures frequent enough to require constant medical attention, alter life style and be intractable to optimal therapy.* It is, however, essential to document optimal therapy before a patient is diagnosed to have intractable or resistant seizures. They comprise about 10-20% of childhood epileptics.

Intractable epilepsy implies seizures that remain uncontrolled for years despite 'relevant' therapy (3). It clearly links refractoriness to adequacy of therapy. Medical treatment is considered inadequate until antiepileptic drugs (AEDs) have been used at maximum tolerated doses regardless of blood levels. Therefore, intractable epilepsy can be divided into true intractable epilepsy in which newer AEDs and surgery have an increasing role and pseudo-intractable epilepsy which is truly inadequately treated epilepsy in which clinical trial with first line AED's are warranted. The latter constitutes a much larger proportion of resistant seizures.

The first concern should be to document whether all episodes that are being considered as seizures are true seizures or not (4). It is not infrequent to have psychological disorders, syncope, sleep and behavior problems misdiagnosed as seizures. Non-epileptic events co-exist in epileptics and confuse the clinician. In adolescents and children with mental handicap, episodic behavioral disturbances are likely to present diagnostic difficulties in almost a quarter of the patients (3). It is important to distinguish the number of true seizures being experienced before labelling the epilepsy as intractable (5). *A close supervision of the attack, circumstances of the event, EEG and video monitoring and serum prolactin levels are parameters that help in making the precise diagnosis.*

The other crucial question is accuracy in diagnosis of type of seizure (6). The therapeutic implications of misdiagnosis of the type of epilepsy are grave, *e.g.,* absence seizures and complex partial seizures are often differentiated imprecisely and etho-suximide, an effective anti-absence drug, prescribed in complex partial seizures without benefit. The converse is true about carbamazepine. Similarly, a misdiagnosis of myoclonus can cause of lack of response to drugs like carbamazepine or phenytoin. In such patients benzodiazepines, sodium valproate or ACTH are essential. *Therefore, accurate diagnosis and appropriate anti-convulsants are necessary before labelling the seizures resistant (6).*

Despite accurate diagnosis and appropriate AED, seizures may *fail to respond due to inadequate dose, irrational drug combinations or even overdoses of AEDs (6).* With monopharmacy of AEDs, drug doses can be gauged by dose in relation to body weight, drug levels and appearance of clinical or toxic side effects. It is important to mention here that AEDs do not follow a rigid

rigid dose schedule. The doses are more flexible, *e.g.,* earlier sodium valproate was used up to a maximum dose of 30 mg/kg body weight, while in recent trials doses up to 100 mg/kg body weight have been used without clinically deleterious side effects. A very strict adherence regarding maximum dose used may, therefore, lead to good first line drugs being discarded. However, it is important to corroborate the use of high doses of AEDs with plasma levels and clinical side-effects so as to get the maximum benefit. In polypharmacy, drugs doses are more difficult to handle specially when large doses are involved and the norms for blood levels are more difficult to interpret.

Indiscriminate increase in doses of antiepileptic drugs in uncontrolled seizures does not always prove beneficial. *Excessive medication* may also result in rebound seizures, a fact clearly demonstrated with phenytoin (7). Prolonged use of antiepileptic drugs can also lead to tolerance or auto-induction resulting in drop in blood levels of AEDs and precipitation of seizures. This is not uncommon with benzodiazepine group of drugs. Occasionally drugs like carbamzepine are known to precipitate seizures.

Drug compliance is the pillar of antiepileptic therapy. *Irregular therapy* is one of the most important causes of drug failure (3). Non-compliance may result from financial constraints, side-effects, denial, getting misled by alternate modes of therapy and as a voluntary act to provoke seizures for seeking gains. It cannot be over emphasized that regularity is the mainstay of epilepsy therapy and all efforts must be made to ensure it. It is not uncommon for patients to deny irregularity in intake of the drug. This fact often needs to be corroborated by random blood level estimations.

There are some epilepsies which due to their intrinsic nature are more resistant to therapy. Lennox-Gastaut syndrome is a classical example. It is an intractable myoclonus of early childhood which is associated with mixed seizures, EEG changes and intellectual deterioration. This accounts for *70% of intractable epilepsies of childhood (3). The next in frequency are partial complex seizures.* These may occur in association with temporal lobe sclerosis following a variety of insults.

At the onset of therapy, several factors may predict a poor response, organic damage, onset in infancy; brain damage; mixed seizure types; multiple seizures; long duration of uncontrolled epilepsy; abnormal EEG; and poor psychological background.

A practical therapeutic approach for management of children with intractable epilepsy includes the following aspects:

Appropriate Drug Dosing

The AED must be appropriately chosen depending upon seizure type and age. The dose should be built up gradually. If the correct drug is being received, the dose should be increased gradually till the maximum tolerated levels (3). The maximum tolerated level is identified by the appearance of toxic side effects with a slight increase in dose. A slight dose reduction from this level often controls seizures. This level is frequently above the maximal prescribed drug dose based on body weight. It also often has no correlation with the dose dictated by the blood level. Adding another drug as a first step is irrational unless the above has been tried.

Alternate First Line Drug Treatment

When the initial first line AED is ineffective, it is better to change to another drug and try it similarly till the maximum tolerated dose. The first drug may be gradually withdrawn it the clinical condition permits (3).

Addition of Second Drug

The next possibility is addition of a second drug. This controls seizures in about 20% and reduces them in about 50% patients provided rational combinations are used (3). It is difficult to maintain adequate drug levels or be totally guided by blood levels when polypharmacy is being tried. However, adequate levels of at least one agent should be achieved. The mechanism of improvement by addition of a small dose of a second drug is not clear.

Non-response to combination therapy should be reinvestigated for etiological factors. The other management possibilities in such subjects include: addition of adjunctive therapy, newer AEDs and surgical intervention, depending upon seizure characteristics and etiology. Specialized tests like MRI, SPECT, HmPAO and PET scans may pin-point hypo-or hypermetabolic zones and also to identify surgically resectable lesions.

Additional Drugs

Addition of a small dose of benzodiaz-epines *{e.g.,* clonazepam) is useful especially for generalized seizures and myoclonus (6). Intermittent intrarectal diazepam prophylaxis during periods of susceptibility (febrile states) may help to curtail seizure recurrence (7). Other possibilities include addition of acetazolamide for a 2-3 week period, and intravenous immunoglobulin, ACTH or corticosteroids for resistant infantile spasms.

Recognition of Precipitants

Provoking or seizure precipitating events like fever, dyselectrolytemia, lack of sleep, hypoglycemia, intercurrent illness and drugs that interact with AEDs should be avoided in all patients. In rare patients drugs not only produce side effects, they may also precipitate seizures (3).

Newer Anti-Epileptic Drugs

Many new agents have been tried in the recent past for control of various types of epilepsies. The more widely used agents among them include vigabatrine, lamotrigine, gabapentin, felbamate and oxcarbazepine. Vigabatrine acts through the GABA pathway. It is recommended as add-on therapy for partial and secondarily generalized epilepsy and appears promising for therapy of infantile spasms (10). Lamotrigine reduces neuronal excitation via the sodium channel pathway and is useful for refractory partial and generalized seizures. The drug has potential use as a broad spectrum monotherapy agent (11). Gabapentin resembles GABA and acts by binding to specific sites in the CNS. Currently it is utilized as add-on therapy for refractory partial epilepsy (12). Its use in pediatric practice is not as well documented as the other two aforementioned drugs.

Felbamate is a drug akin to meprobamate with an undefined mechanism of action. It has proved useful in partial epilepsy and is of some benefit in Lennox Gastaut syndrome. Recent reports of aplastic anemia have aborted its clinical use (13). Oxcarbazepine is a keto-derivative of carbamazepine with less auto-induction and interaction with other AEDs. The drug proved useful in partial and generalized tonic clonic seizures and may be a good substitute for carbamazepine (14). It may be prudent to state that the role of the newer AEDs needs to be authenticated by future larger

trials and their prescription as the first line drugs is currently undesirable.

In conclusion, it is important to be sufficiently aggressive in investigating a patient with recurrent seizures, especially if they are of recent onset. Intractable seizures may result in progressive neurological and intellectual deterioration. A good history, modern investigative technology and resort to appropriate AEDs are essential. A physician should realize the limitations of medical therapy in patients with intractable seizures, and investigate them for the presence of surgically resectable lesions. This multipronged approach will help to achieve better seizure control, reduce secondary brain damage and improve life style of epileptics.

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REFERENCES

1. Sillanapaa M. Children with epilepsy as adults-Outcome after 30 years of follow-up. Acta Paediatr Scand (suppl) 1990, 368: 1-78.
2. Livingston S, Eisner V, Pauli L. Minor motor epilepsy, diagnosis, treatment and prognosis. Pediatrics 1958, 21: 916-928.
3. Aicardi J. Clinical approach to the management of intractable epilepsy, Dev Med Child Neurol 1980, 30: 429-440.
4. Riley TD, Roy A. Pseudoseizures. Baltimore, William and Wilkins, 1982, pp 49-63.
5. Rothner AD. Not everything that shakes is epilepsy. The differential diagnosis of paroxysmal nonepileptiform disorders. Cleve Clin J Med 1989, 56: 206-213.
6 Eadie MJ, Tyrer JH. Anticonvulsant Therapy, Pharmacological Basis and Practice, 3rd edn. Edinburgh, Churchill Livingstone, 1989, pp 134-169.
7. Levy LL, Fenichel GM. Diphenylhy-dantoin activated seizures. Neurology 1965, 15: 716-722.
8. Farrell K. Benzodiazepines in the treatment of children with epilepsy. Epilepsia 1986, 27(suppl 1): 545-551.
9. Oles KS, Peury JK, Cole DLW, Howard G. Use of acetazolamide as an adjunct to carbamazepine in refractory partial seizures. Epilepsia 1989, 30: 74-78.
10. Rey E, Pons G, Olive G. Vigabatrin- clinical pharmacokinetics. Clin Pharmacokinet 1992, 23: 267-268.
11. Broadie JM. Lamotrigine. Lancet 1992, 339: 1397-1400.
12. Fromm GH. Gabapentin-Discussion. Epilepsia 1995, 35(suppl 5): 577-580.
13. Brodie MJ. Felbamate-a new antiepileptic drug. Lancet 1993, 341: 1445-1446.
14. Scwabe S. Oxcarbazepine. Clinical devel-opment program. Epilepsia 1994, 35(suppl 5): 51-52.

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