



Anti-Epilepsy Drugs And Their Adverse Effects

Introduction

About 70% of people with Tuberous Sclerosis will have epilepsy. Epilepsy in Tuberous Sclerosis can be very difficult to control and seizures can change their nature with time. Many people will be on permanent anti-epilepsy drugs and often take a combination of drugs which control their seizures either totally or in part. Many people with TS on anti-epilepsy drugs will have learning difficulties and so it is important that their parents and other carers are aware of the unwanted effects that can be produced by these long term drugs. Fortunately the side-effects of the newer drugs, such as sodium valproate and carbamazepine and lamotrigine which many people take nowadays, are less than the side-effects of the older drugs. Sometimes behaviour can be affected by changing the anti-epilepsy medicine. (See Fact Sheet No 13 by Dr M Brodie).

Most doctors now feel that if possible one drug only should be tried to control epileptic seizures. When other drugs are added there is a tendency for the drugs to interact which may make management more difficult. In particular phenytoin (Epanutin) has a very narrow range between the 'therapeutic' (effective) dose and the higher 'toxic' dose and therefore should be monitored. In addition to blood level tests it is now possible to test for levels of some drugs in the saliva, and this may be preferable in a learning disabled hyperactive child.

An adverse effect of the long-term use of these drugs can be hypocalcaemia or even osteomalacia (rickets) caused by Vitamin D deficiency. Children with TS have been reported to be even more vulnerable to these effects than other children with epilepsy. In some cases, children fractured bones easily when they fell or it became difficult for them to walk because of weak bones. The drugs mainly

responsible for Vitamin D deficiency are phenobarbitone, carbamazepine primidone (Mysoline), and phenytoin. These drugs may also interact with contraceptive pills, so pills with higher hormone levels may be needed.

As a child grows seizures may change and it is important not to continue treatment for one type of seizure when the child may have outgrown them and require a different form of medication. This is important with infantile spasms. The drug of choice nowadays is vigabatrin (Sabril), but because of the associated risk of visual fixed defects it should be removed once the risk of infantile spasms has gone. Similarly, with infantile spasms that may have been treated in infancy with nitrazepam or clonazepam for many years beyond the time when the spasms have ceased and another form of myoclonic epilepsy is being experienced. Benzodiazepines have sedative properties and can produce fatigue, dizziness, drowsiness and ataxia (unsteadiness of standing or walking). Large doses may interfere with a child's development and parents need to consider whether total seizure control or a more aware child is their most important aim.

The effect of drugs varies a great deal between patients and there is no one drug that has been found to be universally effective in children with TS. Some are well controlled on a drug that has caused great problems for another person or vice versa. In reading the information about drugs remember that most children do not develop unwanted effects. Every person reacts differently to a drug so it is a matter of keeping an eye open in case problems arise. Try to establish a good working relationship with your child's doctor. Remember, you are your child's best advocate.

Drug treatment for epilepsy falls into two broad areas: people with newly diagnosed epilepsy and those who have failed to respond or developed side effects to the initial drug treatment.

Before choosing or changing an anti-epileptic drug, it is important to classify the type of seizure disorder. Simplistically the types of epilepsy seen

in Tuberous Sclerosis can be divided into two types:

1. Symptomatic generalised epilepsies where the seizures are a symptom of the underlying brain disorder. When an EEG is done the abnormal electrical activity begins all over the brain.
2. Localisation related epilepsy (focal, partial epilepsy). The abnormal electrical activity begins in one area of the brain and spreads.

Management of patients with continuing seizures

If seizures are predictable then drugs such as clobazam can be very useful, but if given daily, tolerance develops. When used appropriately such as for seizures that cluster around the time of menstruation or when one seizure is followed by a series either that day or the next, clobazam tailored to the individual needs may greatly improve seizure control.

As the response to an anti-epileptic drug is not predictable in any individual it is best to make a choice after weighing up the side effects. Additional factors such as ease of use are important, also drug interactions, (for example with an oral contraceptive pill or other anti-epileptic drugs), pregnancy planning or any pre-existing diseases.

If it is necessary to add in a second drug, it is best gradually to build up the dosage until either seizure control is achieved or side effects develop. Once the recommended dose is reached, if there is no improvement within one to two months then the new drug could be reduced and stopped and an alternative tried.

Commonly used Anti-Epileptic Drugs and their reported adverse effects

Carbamazepine (Tegretol). This is used for generalised tonic-clonic (grand mal) and all partial seizures including temporal lobe seizures. It has little or no beneficial effect on other types of seizure and can make myoclonic seizures worse. Doses should be gradually built up to avoid adverse effects. These can include nausea, vomiting, headaches, double vision, poor co-ordination and drowsiness which may also occur at too high a dosage. The commonest problem is a rash which stops when the drug is withdrawn. More even blood levels are produced by the slow release form

(*Tegretol Retard*). **Oxcarbamazepine** is related to carbamazepine. Because it is metabolically simpler, its use may have fewer complications.

Ethosuximide (Zarontin) This drug is used for petit mal absences which are unlikely in TS. Ethosuximide is a well tolerated drug. As well as apathy and drowsiness, mild euphoria has been reported as an adverse effect.

Phenytoin (Epanutin) Again this is a widely used and effective drug. It may be called *Dilantin* outside the UK. As mentioned before it should be monitored when used with other drugs, as excessive amounts can make seizures worse and cause bizarre behaviour. Toxic signs to watch for are nystagmus (involuntary eyeball jerking), double vision and ataxia. Unwanted effects of phenytoin include gum overgrowth and coarsening of facial features. An excessive hairiness may also be produced which may be unacceptable, particularly in girls. Insomnia, nausea and a skin rash have also been reported. At high doses there may be behavioural disturbances and lack of drive. Vitamin D deficiency may occur. It is teratogenic and a higher dose oral contraceptive pill is needed.

Phenobarbitone This is one of the earliest drugs and has been used for all forms of seizures. Babies with TS may be given phenobarbitone if their first seizures are not infantile spasms. In young children it has the 'paradoxical' effect of irritability, aggressiveness and overactivity whereas adults become sedated. In children it can also have a dulling effect on attention and perception and produce drowsiness, vertigo, headache and nausea. Skin rashes can occur and Vitamin D deficiency. In general, like phenytoin, phenobarbitone has been largely replaced by sodium valproate and carbamazepine.

Primidone (Mysoline) Primidone breaks down in the body to phenobarbitone and therefore should not be used in combination with that drug. Much of what can be said about phenobarbitone also applies to primidone. It has a higher incidence of side effects compared to phenobarbitone.

Sodium Valproate (Epilim) This is widely used in many forms of epilepsy and produces little or no sedation taken alone. It is not recommended for women of child-bearing age if they want a family. Increased appetite can produce obesity. There may be temporary hair loss when the drug is first taken and rarely the hair regrows with curls or

waves. Liver toxicity occurs in a small number of cases (mainly developmentally delayed children with metabolic disorders).

Gabapentin (Neurontin) is effective for partial seizures and is one of the easiest of the new drugs to use as it has few side effects and no interactions with other anti-epileptic drugs. The main problem are frequency of dosage (three times/day) and if the person is in kidney failure a lower dose has to be used. The commonest side effect encountered is dizziness, which often begins on initiating therapy and occasionally weight gain. Gabapentin does not interact with the oral contraceptive pill.

Lamotrigine (Lamictal) is a first line drug for the generalised epilepsies and a useful drug for partial seizures. Its main problems are the interactions with other anti-epileptic drugs (necessitating different dosage schedules) and rash. However, it appears to have some advantages in being a broad spectrum anti-epileptic drug, effective in both partial and generalised seizure disorders and with a low side effect profile. Lamotrigine does not interact with the oral contraceptive pill.

Vigabatrin (Sabril) is an effective anti-epileptic drug and is the drug of choice for infantile spasms. Interestingly, research in the USA shows that it is rendered less effective if other anti-epileptic drugs have already been tried (although if the first drug has failed then the epilepsy is likely to be more resistant anyway). However in adults it does have high incidence of particularly psychiatric side effects (anxiety, depression and psychosis). Problems with vision have been reported recently. These problems have limited its use, although many patients have found it a very valuable anti-epileptic drug. If someone wants to continue taking Vigabatrin it is recommended that they have their visual fields checked every 6 months. This may be difficult or impossible if the person has a learning disability.

Topiramate (Topamax) is a very effective anti-epileptic drug but its usefulness is limited by its side effects, particularly the problem of mental slowing which may appear in up to 25% of people. Weight loss can also be troublesome and there is risk of kidney stones. It interacts with the oral contraceptive pill.

Tiagabine (Gabitril) is a drug which appears effective in people with partial seizures,

particularly those who have responded to Vigabatrin. At present it appears from clinical trials to have a lower side effect profile than Vigabatrin and may provide a useful alternative to Vigabatrin although no direct comparative studies have been performed. The commonest side effect encountered is dizziness. Dosage needs to be adjusted in cases of impaired renal function.

Oxcarbazepine (Trileptal) is a recently licensed anti-epileptic drug for partial seizures. Its main side effects are rash and a low sodium in the blood. It is structurally related to Carbamazepine but has less side effects.

Levetiracetam (Keppra) is licensed as add on for partial seizures. However it appears to be very effective in the treatment of generalised epilepsies particularly in those with learning disabilities. Its main side effect is drowsiness but occasionally behavioural problems are seen.

Corticosteroids (ACTH, Prednisone) These drugs are mainly used for infantile spasms. They can also be used for otherwise intractable seizures, but in either case they are used under strict medical supervision. Use is short-term because of the risk of physical complications with long-term use. Withdrawal from corticosteroids should be gradual.

Benzodiazepines These drugs include clobazam (Fristium), clonazepam (Rivotril), diazepam (Valium), midazolam and nitrazepam (Mogadon).

Clobazam (Frisium) It is usually used in combination with other anti-epilepsy drugs. As mentioned above, clobazam tailored to the individual needs may greatly improve seizure control, but if used daily tolerance develops. It can be very helpful when used intermittently.

Clonazepam (Rivotril) has been used for various forms of epilepsy, particularly for infantile spasms, myoclonic epilepsy and absence attacks (petit mal). It can have a sedative effect in young children which might be avoided by gradually introducing the drug. It can also cause salivary and bronchial hypersecretion (dribbling and chestiness). Unwanted effects are ataxia and fatigue and therefore a young child's development may be delayed until the body gets used to the drug. Extreme irritability, excitement, aggression and hyperactivity have all been reported in children with TS on clonazepam.

Diazepam (Valium). This is a very useful drug for prolonged seizures and many parents keep “Stesolid” for rectal administration if their child is liable to status epilepticus attacks. It is best reserved for emergency situations. It can also be used to treat non-convulsive status epilepticus.

Buccal Midazolam This is a useful alternative to rectal diazepam for treating acute seizures or status epilepticus. The medication is inserted in the mouth, just under the cheek, so is more socially acceptable than the rectal alternative. The disadvantage is that it is unlicensed and has not been properly evaluated in adults.

Nitrazepam (Mogadon). This is used to promote sleep and as an anti-epilepsy drug for infantile spasms. Adverse effects are similar to clonazepam. Again addiction occurs readily and great care must be taken when withdrawing from the drug.

ANY CHANGES IN DRUGS SHOULD BE MADE UNDER MEDICAL SUPERVISION

Surgery and other Non Drug Therapy

It has been realised that some patients will never become seizure free on currently available anti-epileptic drugs and surgery is an important treatment option. In people with TS it may be possible to remove a cortical tuber if it is acting as a focus for epileptic seizures. However, the assessment needed is complicated and requires a multi-disciplinary team which is only available at a few neuroscience centres in the United Kingdom. Other rarer operations can occasionally be beneficial in people with TS and severe epilepsy.

Other new therapies are now available eg vagal nerve stimulation and other non-drug methods of stopping seizures (such as utilising ways of stopping seizure activity progressing in patients who have prolonged auras and the ketogenic diet). These are only of value for a small number of patients and are still under evaluation.

Useful addresses:

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National Society for Epilepsy, Chesham Lane, Chalfont St Peter, Gerrards Cross, Bucks, SL9 0RJ. Helpline: 01494 601 400

F.A.B.L.E. Charity, 9-13 Ashgate Road, Sheffield, SL10 3BZ. Helpline: 0800 267 8894

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