MANAGEMENT OF EPILEPSY

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Figures for the incidence of epilepsy in Malta are not available. The overall figure for epilepsy given by the Royal College of General Practitioners (Reid 1960) is 4.82 per 1,000 population. As there is no reason to expect any difference in the incidence in these Islands, one can expect that there are at least 1,500 epileptics in Malta. This would mean that all general practitioners would, at some time, come across a patient with epilepsy.

Before considering the various drugs available for the treatment of epilepsy, it is worth highlighting the following points.

Epilepsy is not one homogeneous condition, but many.

Some patients with epilepsy have very infrequent attacks while others may have a considerable number of attacks per day. The latter group may prove to be more difficult to control.

While on the one hand it is common practice not to treat with anti-convulsants patients who have had a solitary fit, there is some suggestion on the other hand that early treatment of fits prevents epilepsy from becoming chronic. Lennox in 1960 [1] stated that 3 seizures in the space of 6 months was about all that one should tolerate before starting drug therapy.

Once a decision is taken that a patient needs treatment, one has a number of drugs to choose from. Current opinion today favours the use of one drug alone and to use it efficiently (Shorvon et al 1978) [2] and (Chadwich et al) [3].

PHENOBARBITONE

This was the first effective anti-convulsant and has been in use since 1912. Today this drug has, by and large, been superseded by others and I tend to use it very little in my practice.

There is no doubt that Phenobarbitone is effective in controlling tonic-clonic seizures. However, it has a high failure rate in controlling partial seizures. The only advantages that Phenobarbitone has over other drugs are the minimal gastro- intestinal side-effects and its low cost. Dose-related side- effects include drowsiness, ataxia, lethargy and slurred speech. Idiosyncratic side-effects include hyperactivity, altered mood, impaired cognitive function, altered calcium metabolism and skin rashes. Measurement of serum levels is helpful mainly to check on patient's compliance; otherwise the clinical value of such estimations is limited.

PRIMIDONE (MYSOLINE).

This is metabolised by the liver into two active components, namely phenobarbitone and phenylethylmalonamide (PEMA). There is some evidence that both unchanged Primidone and PEMA have some anti-convulsant activity in their own right. If, however, the major anti-convulsant activity of Primidone is due to the derived Phenobarbitone, then there is little advantage in using Primidone rather than Phenobarbitone. From clinical studies (Mattson et al NEJM) [4], Primidone is equally effective as Phenobarbitone in controlling tonic-clonic seizures, and equally ineffective in controlling partial seizures. There is little clinical use in measuring serum levels other than to check on compliance.

PHENYTOIN (EPANUTIN)

Nowadays, Phenytoin is very often used as first line treatment. It is equally effective in controlling tonic-clonic seizures as Phenobarbitone, but superior to Phenobarbitone as regards partial seizures. The pharmacokinetics of Phenytoin are today very well understood. The drug has a long half life, and the whole dose can therefore be given once daily to adults and twice daily to children. This no doubt improves patients' compliance. Measurements of serum levels are mandatory, owing to the fact that the relationship between the serum level concentration and the dose administered is an exponential one; and therefore small increments in the dose could produce toxic levels. For this reason one is advised to increase the dose by 50 mg. increments each time when necessary. Once a steady state is achieved and Phenytoin is used as sole medication, serum levels need not be measured more than once yearly. Serum measurements again become mandatory if the brand of Phenytoin is changed. Dose-related side-effects included nystagmus, diplopia, ataxia, nausea, vomiting and drowsiness. One has to enquire about these symptoms and look for the appropriate signs at routine follow-up. Idiosyncratic effects include acne, rash, gingival hyperplasia, megaloblastic anaemia, bone marrow depression, abnormal results of liver function tests, altered calcium metabolism and hirsutism. If these side-effects occur, the drug should be replaced. Dysmorphic side-effects occur frequently (22%) (Mattson et al) [4] and therefore one tends to avoid this drug in children, adolescents and women.

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An advantage of Phenytoin is definitely its low cost as compared to that of other major anti-convulsants.

Phenytoin is the drug of first choice in an adult who presents with tonic-clonic seizures or partial seizures.

CARBAMAZEPINE (TEGRETOL)

Since its introduction for use in epilepsy in 1963, this agent has become an eminent first line management drug mainly due to its low toxicity and simplicity of use. The only significant disadvantage is its high cost. Today with the introduction of the Controlled Released Tegretol, twice daily medication is possible, and this will definitely enhance compliance.

Carbamazepine is introduced at a low dose, and then steady increments in dose are made at weekly intervals, until a maximum of 1,600 mg. daily is reached. Very often much lower doses may be sufficient. The importance of gradual increments in dosage is to reduce the incidence of early side-effects which are nausea, drowsiness, ataxia and dizziness. Other dose-related side- effects are nystagmus, diplopia, blurred vision and headaches. Idiosyncratic side-effects include transient leukopenia, rash, fluid retention and very uncommonly aplastic anaemia.

Carbamazepine is slightly more effective than Phenytoin or Phenobarbitone in controlling generalised tonic-clonic seizures; it is about 3 times more effective than Phenobarbitone and twice more effective than Phenytoin in controlling partial seizures. (Mattson et al) [4]. Carbamazepine also had the lowest incidence of side-effects when compared to Phenobarbitone, Phenytoin and Sodium Valproate used as monotherapy. The figures for drug withdrawal in childhood because of side-effects, are as follows:-
Phenobarbitone 30%; Phenytoin 23%; Sodium Valproate 15%; and Tegretol 8% (Forsythe and Sills) [5].

Determination of serum levels for Carbamazepine would not appear to be very useful clinically. Clinical assessment and observation of fit reduction would be enough.

Carbamazepine is one of the major anti-

convulsants (although it does not help all patients). It is to be considered first line management for generalised tonic-clonic seizures in children and women of child-bearing age, and for all patients with simple seizures and partial seizures with complex symptomatology (i.e. Temporal Lobe Epilepsy).

SODIUM VALPROATE (EPILIM)

This was introduced in 1974 and is today considered as one of the three main line therapeutic agents (i.e. with Phenytoin and Carbamazepine). Sodium Valproate has a "broad spectrum" of anti- epileptic activities in adults and children. It is generally well tolerated. Dose-related side-effects include nausea, vomiting, weight gain, tremor, anorexia, indigestion, and heartburn, while idiosyncratic side-effects include rash, bone marrow depression, hepatotoxicity, alopecia and pancreatitis and rarely amenorrhoea. Dosage schemes are simple: in adults treatment is started at a dose of 200 mg. twice daily, with regular increments up to a maximum of 2,600 mg. daily, depending on clinical responses. In children, the maximum dose is 30 mg./Kg. per day. The introduction of enteric coated Epilim has enabled the total daily dosage to be given in two divided doses, thereby enhancing compliance.

There does not appear to be any necessity for routine serum estimation. This however may be useful when poor compliance or side-effects are suspected or when poor seizure control is present. Sodium Valproate was found to be equally effective as Phenytoin in adult onset epilepsy (Turnbull et al) [6] while Loiseau [7] concluded that Valproate was at least equally effective as Carbamazepine in controlling partial seizures. Sato et al [8] concluded that Valproate was as effective as Ethozuximide in controlling petit mal attacks (i.e. 3 cycle/sec spike and wave discharges on E.E.G. with clinical accompaniments). Covanis et al [9] found that myclonic seizures were adequately controlled (84%) by Valproate. Finally Jeavons et al [10] concluded that Valproate will control up to 60% of Photosensitive epileptic attacks.

Valproate is therefore indicated as first line management in children and young males with generalized tonic-clonic seizures, petit mal, photosensitive and myoclonic epilepsy. Owing to recent reports of an association between neural tube defects and Valproate administration in pregnancy Valproate should perhaps be avoided in post-pubertal adolescent females and women of the child-bearing age.

ETHOSUXIMIDE (ZARONTIN)

Ethosuximide together with Valproate is one of the two drugs of choice in petit mal. It is a relatively safe drug. Dose-related side-effects include nausea, vomiting, anorexia, headache, fatigue, lethargy, dizziness and hiccups; while idiosyncratic side-effects include, rash, blood dyscrasias, periorbital oedema, renal dysfunction and liver dysfunction.

The usual dose of Ethosuximide is 750 mg. given in three divided doses. As tonic-generalized seizures often co-exist with petit mal attacks, a second drug may have to be used together with Ethosuximide. In this situation, Epilim would be a superior drug to use as it is effective for both conditions.

Blood level estimation is not particularly helpful clinically.

CLONAZEPAM (RIVOTRIL)

Clonazepam is a benzodiazepine derivative and is generally used as a second line treatment for petit mal and generalized tonic-clonic seizures. Dose-related side-effects include drowsiness, sedation, ataxia, hyperactivity and irritability; while idiosyncratic side-effects include hypersalivation and increased bronchosecretion.

WHEN SHOULD A SECOND DRUG BE INTRODUCED?

Monotherapy, if used judiciously, can give very favourable results in a large number of patients. A second drug is to be added only if control has been unsatisfactory. One has to remember that treatment with more than one drug alters the pharmokinetics of individual drugs. Unsatisfactory control does not mean a one-off seizure, or the occurrence of one seizure a year, where previously the patient was having up to 10 per year or more. One must resist the pressures by patients or their relatives to change medication or add something new at this stage.

WHEN SHOULD MEDICATION BE STOPPED?

This is a difficult problem. It is not uncommon to find patients who have been fit free for 20 years and are still on anti- convulsants! Generally speaking if the patient has been seizure- free for over 4 years, has had a normal E.E.G., and the attacks were not focal or due to an underlying organic lesion, and the patient did not have seizures for a long time before control was achieved, then withdrawal of medication should be considered. This should be done gradually and over a long period of time, such as 12 months. The recurrence rate for children is about 1 in 4 while that in adults is 1 in 3. The advantages of stopping medication should be obvious, and these include unnecessary expense and eliminating the possible long-term side-effects of drugs, and in female patients because of the possibility of pregnancy.

ANTI-CONVULSANT THERAPY IN PREGNANCY.

Anti-convulsant therapy is essential in pregnancy, if the mother has active epilepsy. Prolonged seizures may be more harmful to mother and foetus than the risks of anti-convulsants. While it is true that there is an incidence of neonatal malformation of about 2 to 3 times the normal in babies of epileptic mothers on anti-convulsants, no specific drug can be implicated. These malformations include facial clefts, congenital heart disease, and malformations of the urogential system (mainly hypospadias).

With the exception of Sodium Valproate, there is no reason to change pre-pregnant anti-convulsants. Monitoring of serum anti-convulsants is helpful in pregnancy, as an upward dose adjustment may be necessary. An increase in bleeding tendency has been reported in pregnant epileptic women on anti-convulsants. This is presumed to be due to deficient formation of Vitamin K dependent coagulation factors. For this reason Vit.K. is given to the mother prior to delivery and to the baby at birth [11].

Breast-feeding is not contraindicated in epileptic mothers on anti-convulsants. If epilepsy occurs for the first time in pregnancy, Carbamazepine is the treatment of choice.

THE TREATMENT OF MAJOR STATUS EPILEPTICUS

This is par excellence one of the more acute emergencies in neurological practice, with a mortality of circa 20% (Oxbury & Whitty) [12]. Patients should be treated in an Intensive Care Unit. Therapy should be administered intravenously in high doses, and repeated as necessary.

Diazepam (Valium) is given in a dose of 10 mg. i.v. over a 2 minute period, and usually terminates status. Higher doses however may be required in adults. (Children require smaller doses). Repeated doses may be essential.

Chlormethiazole (Heminevrin) is next used if diazepam fails. This agent is given as an I.V. infusion of 0.8% solution. The rate is to be adjusted according to clinical response.

General anaesthesia and curarization is required if the above measures fail.

The pre-status anti-convulsants should be continued, or, if the status occurred as the first manifestation of epilepsy, then Phenytoin or Carbamazepine should be started immediately, together with the above.

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