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Anti-epileptic drugs: a guide for the non-neurologist

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ABSTRACT – Epilepsy is the most common serious chronic neurological disorder affecting between 0.5% and 1% of Western populations.[1] Most patients take anti-epileptic drugs (AEDs) for years if not decades, and are commonly admitted to hospital with seizures. Many have symptomatic epilepsy, arising as a consequence of another disorder, for example a brain tumour. General practitioners, emergency physicians and most hospital teams (especially general medicine) commonly encounter difficulties surrounding AEDs yet often require assistance from neurology services. This can be difficult when neurology services are not on-site or easily available. This article gives a practical overview of difficulties relating to AEDs and their management, with the focus on problems commonly encountered by non-neurologists. These include the patient who is acutely unwell, pregnant or elderly; AED side effects and drug interactions; status epilepticus and AED blood levels.

KEY WORDS: anti-epileptic, anti-convulsant, contraception, drug levels, elderly, general medicine, generalist, interactions, pregnancy, side effects

Introduction

The history of anti-epileptic drugs (AEDs) is punctuated by a mix of accident and design, starting with the use of bromides in the 1850s and phenobarbital and phenytoin in the first half of the 20th century.[2] The 1960s and 1970s saw sodium valproate (valproate) and carbamazepine become the standard treatments for epilepsy, which they still are. A hiatus occurred until the 1990s when the newer generation of AEDs began to appear, turning the previously implicit simplicity of AED choice into a complex affair, with 21 AEDs currently licensed in the UK.[3]

Ethical considerations preclude the use of double-blind placebo controlled trials for newer AEDs as monotherapy. As such they gain licences for adjunctive therapy in patients with uncontrolled focal epilepsies from short placebo controlled trials determining the 'responder rate' for a seizure reduction of 50% or more. These refractory patients do not represent the population with epilepsy and so there are limitations in applying the evidence from these trials in the real world. Post-licensing studies examine longer-term effects, such as the visual field constriction later found with vigabatrin.[4] Post-licensing trials showing non-inferiority of newer AEDs to 'standard' AEDs when used as monotherapy led to additional licenses for this indication.

Initiation of anti-epileptic drugs

The choice of AED following a new diagnosis of epilepsy can be complex and is affected by age, co-morbidity, concomitant medication, possibility of pregnancy and the individual's epilepsy classification. The diagnosis of epilepsy and initiation of treatment should only be made by, or in conjunction with, a specialist trained in the management of the condition.[5] Nevertheless, a framework exists for the preferred AED for initial monotherapy, depending on whether the seizures are generalised or focal (with or without secondary generalisation) in onset (Table 1). Importantly, the recent multicentre SANAD study suggests lamotrigine has non-inferior efficacy and is better tolerated than carbamazepine as monotherapy for focal onset epilepsies and it may become the preferred choice.[6] Valproate still remains the best combination of efficacy and tolerability for generalised epilepsies.[7]

Concerns have long been held over whether to commence AEDs following a first unprovoked seizure, a problem commonly faced by many clinicians. Reassuring clarification comes from the MESS study, which showed that starting treatment after a first seizure reduces recurrence at two years but has no benefit on

Table 1. Drugs commonly used in the treatment of epilepsy (as per National Institute for Health and Clinical Excellence guidelines (2004,[5] revision due 2011)).

Drugs used in generalised epilepsies	Drugs used in focal onset epilepsies
First line	***First line***
Valproate*	Carbamazepine (or oxcarbazepine)
Ethosuximide (for absence seizures)	Lamotrigine
Lamotrigine (*may* initiate myoclonus in high doses)	Valproate*
Carbamazepine (*may* worsen absence seizures or myoclonus)	Topiramate
Topiramate	***Second line***
Second line	Levetiracetam
Levetiracetam	Phenytoin (in *acute* situations)
Clobazam	Tiagabine
Oxcarbazepine	Gabapentin
	Clobazam

*Avoid as first choice anti-epileptic drug in women of childbearing age where possible.

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longer-term remission rates, and leads to no reduction in sudden unexplained death (SUDEP) compared with deferred treatment (after two or more seizures).[8] Further results from the MESS study identified three features associated with a high risk of seizure recurrence that might warrant immediate treatment.[9] These were the existence of a pre-existing neurological disorder, an abnormal electroencephalogram (EEG), and occurrence of two or more seizures at presentation. A first seizure always warrants referral to neurology services but the presence of these features might alert the non-neurologist to contact 'on-call' neurology services as treatment may need to be started immediately.

Once an effective monotherapy AED is found (two to three may be tried), over 70% of patients achieve full seizure control.[10] The remainder continue to have seizures requiring two or more AEDs and pose a challenge to neurologists and non-neurologists alike. It should be remembered, however, that misdiagnosis is common, the problems associated with this being beyond the scope of this article.[11]

Anti-epileptic drugs and acute illness

Patients with epilepsy may be admitted to hospital with other conditions, and be declared 'nil by mouth'. This situation needs immediate attention as most AEDs have relatively short half lives, being taken two to three times a day. Their omission can quickly lead to refractory seizures or status epilepticus, especially with barbiturate (mostly phenobarbital) withdrawal. Intravenous (iv) formulations of the patient's usual AEDs are required. Phenytoin, phenobarbital, valproate, levetiracetam and most benzodiazepines are available in iv formulations; lamotrigine, carbamazepine and topiramate are not. Carbamazepine is available for short-term use as a suppository but has limitations in dose and efficacy.[12] Early involvement of neurology is encouraged where necessary (to choose an alternative AED).

A similar problem arises when a patient has decreased consciousness, a poor swallow, or indeed status epilepticus. The overriding principle is that efforts should be made to administer the patient's usual AEDs via the enteral route and it is crucial that a nasogastric (NGT) or a percutaneous endoscopic gastrostomy tube (PEG) is utilised early to accomplish this. Once enteral access is achieved the next AED doses should be given without delay before continuing the usual regime, with consideration of top-up doses if multiple doses have already been missed. The commonly used AEDs are available in liquid formulations. Of particular note is that phenytoin suspension does not have dose equivalence to phenytoin tablets (90 mg suspension = 100 mg tablet) and so caution should be exercised.

Anti-epileptic drug levels – when and why?

Routine measurement of AED levels is not necessary. Doses are adjusted on the basis of clinical information such as seizure frequency and adverse effects, not on the basis of AED levels. Some patients achieve seizure freedom with AED levels below the 'normal' range and some tolerate levels above the 'normal' range without clinical toxicity. National guidance is available on when to check levels; indications include managing drug interactions, confirming clinical suspicion of toxicity and serial measurement to monitor compliance in difficult cases.[5] Phenytoin is the exception to this rule; due to its zero order kinetics small adjustments in dose can lead to large fluctuations in serum concentration meaning blood levels are advised, usually one week following dose changes. However, these levels must always be interpreted in their clinical context.

The only scenario in which the authors would advocate routinely checking AED levels is during status epilepticus where clinical information may not be available in the emergency setting, so long as the results are interpreted correctly when the history is subsequently obtained. Following emergency initiation of iv phenytoin (ie loading dose), serum levels within 24 hours assist in deciding the continuing daily dose. A common contributor to treatment failure in status epilepticus is sub-therapeutic doses of phenytoin.

Side effects of anti-epileptic drugs

Side effects of AEDs often lead to hospital admission and it is easiest to divide these into effects common to all AEDs and those that are specific to a particular drug or drugs. The latter may be acute (dose-related or idiosyncratic) or chronic. Somnolence, nausea and dizziness are common to the majority of AEDs following initiation but often lessen with time or dose reduction.

A rash can develop following initiation of many AEDs and is the reason for the slow titration of lamotrigine. Rashes may range from mild erythema to toxic epidermal necrolysis and so abrupt drug withdrawal and specialist advice are sometimes required. Acute phenytoin, carbamazepine and valproate toxicity can be wrongly attributed to primary neurological disease when patients present with new onset ataxia or diplopia. Oxcarbazepine is often used where carbamazepine has been poorly tolerated. Blood dyscrasias may be seen with carbamazepine, valproate and phenytoin; most often thrombocytopaenia seen with valproate. Valproate is also associated particularly with weight gain, hair loss and a fine tremor, as well as hepatic dysfunction which is usually transient but can progress to liver failure. Valproate is also rarely associated with an encephalopathy in its own right. Enzyme inducing AEDs may cause an asymptomatic rise in liver function tests (LFTs) that does not signify liver dysfunction and does not require action. Topiramate has the often useful side effect of weight loss but is also assosciated with renal stones and glaucoma.

Longer-term effects are subtle and harder to detect. A number of AEDs may lower bone mineral density and so physicians need to be alert to their use in high-risk groups (elderly, steroid use, post-menopausal women). With long-term use phenytoin can have significant cosmetic effects causing gum

hypertrophy, hursuitism and coarse features, as well as a peripheral neuropathy. The British National Formulary is an excellent source of information.[12]

Anti-epileptic drugs and pregnancy

Women with epilepsy who wish to or may become pregnant need to be counselled on the increased risk of major congenital malformation (MCM) associated with fetuses exposed to AEDs, and indeed epilepsy itself. In the UK a register has been in operation since 1996 which forms an ongoing prospective study of all AEDs.[13] Women in early pregnancy (before the outcome is known) should be encouraged to register. Current evidence suggests valproate (6.2%) and polytherapy (6.0%) are associated with the highest MCM rates; carbamazepine (2.2%) is little worse than the background population rate (1–2%).[14] Rates for the newer AEDs are not yet clear and as such all women of childbearing age are advised to take folic acid 5 mg daily to help minimise this risk. When choosing an AED for women of childbearing age valproate is generally avoided where possible, lamotrigine being a commonly used alternative. However, when already pregnant it is often better not to attempt changing AEDs as it may be too late and exposes the mother and child to the additional risks of seizures.

Pregnant women with epilepsy need close monitoring and access to specialist advice. Increasingly in the UK joint clinics are held by obstetricians and epileptologists or epilepsy specialist nurses for these patients. A sensible approach would be to contact the local epilepsy specialist nurse where assistance is required. Stopping AEDs on learning of pregnancy is not recommended although some patients with infrequent seizures may decide to come off their AEDs with specialist supervision during pregnancy. Physiological changes in pregnancy have complex and varied effects on a number of AEDs and dose changes may be needed during pregnancy. This is a situation where management may need to be guided by AED blood levels.

Anti-epileptic drugs and contraception

The most common drug interaction of AEDs is the effect of enzyme inducers (carbamazepine, phenytoin and phenobarbital) on the combined oral contraceptive pill (COCP) (Table 2). These drugs are thought to increase hepatic metabolism of the COCP and so a higher dose of oestrogen is advised. At least 50 mcg and as much as 100 mcg daily may be required but no preparation in the UK contains more than 40 mcg in one tablet and so multiple tablets are required.[15] Still this does not guarantee against contraceptive failure and barrier methods as well as 'tri-cycling' are often recommended in addition. Progesterone-only pills are even worse affected by enzyme inducers and are not recommended. The morning after pill can be used but a double dose is recommended.

Table 2. Anti-epileptic drugs and the combined oral contraceptive pill.

Drugs affecting contraceptive efficacy	Drugs with no effect on contraceptive efficacy
Definite effect (enzyme induction)	Benzodiazepines
Carbamazepine	Gabapentin
Phenobarbital	Levetiracetam
Phenytoin	Pregabalin
	Valproate
Possible effect	Vigabatrin
Lamotrigine	Zonisamide
Oxcarbazepine	
Topiramate (doses >200 mg/day)	

A special situation exists with lamotrigine where the reverse phenomenon is seen. The COCP can reduce lamotrigine levels and so patients may experience increased seizures on starting contraception. An increase in lamotrigine dose is often required and conversely toxic symptoms may occur if the COCP is stopped without changing the dose back.

Twelve weekly medroxyprogesterone injections (depo-provera) are not affected by AEDs and may be used in the normal manner. The same cannot be said for progesterone implants. Intrauterine devices are unaffected by AEDs.

Interactions with anti-epileptic drugs

Interactions occurring between individual AEDs are best managed in the neurology clinic, but important interactions also occur with other drugs that are relevant to all medical specialties.[16,17] The enzyme inducers already mentioned are metabolised by the cytochrome P450 system, as are many other drugs; warfarin and digoxin are two notable examples where drug levels may fall following initiation of an enzyme-inducing AED, with obvious implications for the treatment of other medical conditions (Table 3). The enzyme-inducing AEDs may also exhibit auto-induction whereby after several weeks of initially successful therapy, seizure frequency increases due to increased metabolism of the AED as a consequence of its own enzyme-inducing properties.

AEDs are susceptible to drug interactions as well as causing them. Potent P450 enzyme inhibitors such as erythromycin, clarithromycin and cimetidine can lead to significant increases in serum AED levels. Many antidepressants lower the seizure threshold which has implications for AED doses and antipsychotics antagonise many AEDs, lowering plasma concentrations. Antidepressants, however, should not automatically be stopped if breakthrough seizures occur. Valproate is an enzyme inhibitor and may increase the anticoagulant effect of warfarin. It also increases lamotrigine levels when prescribed concurrently and caution is needed when using the two drugs together; smaller doses and slower titration of lamotrigine are required.[12]

With all these interactions anticipation and avoidance are preferred, but when faced with such clinical scenarios consideration

Table 3. Important interactions with anti-epileptic drugs (AEDs).

Drug	Potential effect
Phenytoin/ carbamazepine (enzyme inducers)	***Reduces levels of*** oestrogens, progesterones, corticosteroids, tricyclic antidepressants, valproate, lamotrigine, topiramate, warfarin, beta-blockers, calcium channel blockers, digoxin ***Levels increased by*** erythromycin, clarithromycin, cimetidine, isoniazid, acetazolamide, amiodarone, diltiazem, verapamil, omeprazole ***Levels reduced by*** rifampicin
Phenobarbital (enzyme inducer)	***Reduces levels of*** carbamazepine, lamotrigine, valproate, phenytoin, corticosteroids, oestrogens, progesterones ***Levels increased by*** valproate, phenytoin
Valproate (enzyme inhibitor)	***Increases levels of*** lamotrigine, carbamazepine, warfarin, benzodiazepines ***Levels increased by*** cimetidine, erythromycin, clarithromycin, isoniazid ***Levels reduced*** by rifampicin
Lamotrigine	***Levels reduced by*** oestrogens, progesterones, carbamazepine, phenytoin, phenobarbital, rifampicin ***Levels increased by*** valproate
Antipsychotics/ antidepressants (SSRI, tricylic, possibly MAOI)	May inhibit anticonvulsant effect of AEDs (increase seizure risk) Enzyme-inducing AEDs may reduce levels requiring increased doses

MAOI = monoamine oxidase inhibitors; SSRI = selective serotonin reuptake inhibitors.

of the potential role of AEDs and drug interactions is the first step in determining and solving the problem.

Anti-epileptic drugs and the elderly

The elderly have the highest incidence of new diagnoses of epilepsy and it is a necessary fact that the majority will have cryptogenic or symptomatic focal epilepsy. They require special consideration for numerous reasons; multiple concomitant medications increase the potential for drug interactions, incidence of side effects increases in the elderly, renal and hepatic function decreases with age and cognitive impairment and compliance issues are more prominent.

Fortunately seizures in the elderly are more easily controlled and so the principles of AED selection shift from choosing the most efficacious agents to choosing those with the least side effects and drug interactions.[18] Consequently, newer AEDs such as lamotrigine and levetiracetam are commonly chosen when treating the elderly, and lower than usual doses are required. Nevertheless many elderly patients remain on historic prescriptions of older AEDs, including barbiturates, and are not uncommonly admitted to hospital as a result. Ataxia and cognitive impairment associated with carbamazepine, phenytoin or valproate may be wrongly attributed to cerebrovascular disease or dementia when trying to explain an individual's decreasing mobility and falls for example. Carbamazepine and oxcarbazepine are also implicated in hyponatraemia, a common reason for hospital admission in the elderly.

Summary

All doctors, particularly those working in emergency medicine, acute medicine, care of the elderly and general practice require a working knowledge of AEDs. The issues of major importance are identifying side effects and drug interactions, special considerations for women of childbearing age and, increasingly, the elderly population. The medical treatment of epilepsy has the potential to impact on any other medical disorder, and vice versa, and so clinicians need to identify and solve problems promptly or ask for timely help where needed. The initiation of AEDs, as well as dose changes, should always be made or supervised by a clinician trained in the treatment of epilepsy.

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