

Can drug resistance in epilepsy be minimized? Challenging commonly held beliefs

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ABSTRACT – Until more efficacious antiepileptic drugs (AEDs) that can tackle the challenge of drug-refractory epilepsy are developed, the best way to minimize inadequate seizure control is to exploit at best available treatments. There are however, discrepancies between commonly held opinions on several aspects of drug therapy, and the body of scientific evidence which exists to support them. This article highlights a few examples, discussing evidence that, contrary to common belief, (i) a significant proportion of patients with newly diagnosed epilepsy respond to concentrations of AEDs below the “therapeutic range” quoted in the literature; (ii) only a small group of patients unresponsive to low to moderate AED dosages become seizure-free after increasing dosage up to the limit of tolerability; (iii) knowledge of mechanisms of AED action can aid in the rational use of AEDs in the clinic; (iv) monitoring serum levels of new generation AEDs can be usefully exploited to improve management, and (v) at least in a subgroup of patients, successful epilepsy surgery cannot be regarded as curative, because seizure control may be dependent upon continuation of AED therapy. It is hoped that increased awareness of these issues could eventually contribute not only to improved clinical outcome, but also to high quality studies in many areas where gaps in knowledge prevent application of truly evidence-based management.

Key words: antiepileptic drug, epilepsy, drug resistance, overtreatment, polytherapy, therapeutic drug monitoring

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Drug resistance is the main determinant of low quality of life in persons with epilepsy, at least in industrialized countries (Schmidt and Löscher 2005). The proportion of patients whose epilepsy is drug-resistant varies depending on the definition of the condition, the study methods used, and the characteristics of the population being studied. However, overall it has been estimated that between 30 and 40% of patients fail to achieve enduring seizure control with availa-

ble antiepileptic drugs (AEDs) (Perucca 1998, Kwan and Brodie 2000a). New generation AEDs have widened our ability to tailor drug choice, but their benefits relate to improved tolerability rather than greater efficacy. Indeed, probably no more than 5-10% of patients with severe drug-resistant epilepsy achieve freedom from seizures when started on a new AED (Walker and Sander 1996, Leppik *et al.* 2005). Until more effective agents are introduced, the goal of reducing the

burden of drug-resistant epilepsy can only be pursued by improving the use of currently available drugs.

The purpose of the present article is to discuss how the management of epilepsy could be improved by reassessing critically some misconceptions. Hopefully, such reassessment could result in more rational drug treatment and, ultimately, more patients achieving sustained freedom from seizures with the fewest possible adverse effects.

Misconception 1: few patients respond to “low” AED doses and “subtherapeutic” serum AED levels

It is widely recognized that the key to therapeutic success in epilepsy goes beyond selecting an appropriate AED; it is critically dependent on the physician's ability to tailor dosage to individual needs (Perucca *et al.* 2001). In some cases, dose individualization is facilitated by measuring serum drug concentrations, a procedure known as “therapeutic drug monitoring (TDM)” (Eadie 1998). Therapeutic failure can result from prescription of insufficient dosages, but there are also cases where apparent drug resistance results from prescription of excessive dosages leading to adverse effects (Kwan and Perucca 2005). If an optimal outcome is to be achieved, the dosage should be the minimum required to produce seizure freedom without unacceptable toxicity.

Dose selection is influenced by a number of factors, including information on the product's data sheet, data from clinical trials, dosing recommendations in review articles and textbooks, personal experience, and feedback from other practitioners. However, these sources do not yield necessarily univocal information on critical details such as optimal starting dosage, titration rate and initial maintenance dosage (Perucca *et al.* 2001). Neither is the situation helped by the fact that the clinical trials used to obtain regulatory approval of AEDs are not designed to identify optimal dosages, and may result in dosing recommendations that are later found to be unsatisfactory (Walker and Sander 1997). Dosage requirements vary depending on age, body weight, type of epilepsy, comorbidities, co-medications, and other factors (Perucca *et al.* 2001). For example, in a large, randomized, flexible-dose trial, the average dosage of valproate required for localization-related epilepsies was about 30% higher than that required to control primarily generalized tonic-clonic seizures (1006 versus 821 mg/day respectively) (Richens *et al.* 1994).

Many patients with newly diagnosed epilepsy achieve seizure freedom at lower dosages than those required to optimize treatment in patients with difficult-to-treat epilepsies. This has been shown elegantly in an observational UK study that included 470 previously untreated patients (Kwan and Brodie 2001). In this study, 84% of patients

achieved seizure freedom at carbamazepine dosages of 600 mg or lower. These dosages may be lower than the initial maintenance dosage utilized by some physicians in various parts of the world.

Similar considerations apply to optimal serum AED concentrations (Perucca and Richens 1981, Schmidt and Haenel 1984, Schmidt *et al.* 1986, Theodore 1992, Eadie 1998). Commonly quoted “therapeutic” ranges of serum concentrations are often derived from studies in patients with severe epilepsy, and are not necessarily applicable to an unselected population. This concept is well illustrated by the landmark study that, in the early 70s, led to the general acceptance of a therapeutic range for phenytoin (Lund 1974). This was a 3-year, prospective assessment of 32 patients with uncontrolled, primarily or secondarily generalized tonic-clonic seizures; 16 of these were on polytherapy. When dosage was adjusted to bring phenytoin levels within the “therapeutic range” of 10 to 20 mg/L, seizure frequency improved dramatically, and 14 patients became free from tonic-clonic seizures. Although the author was careful to point out that “the optimal plasma level varies between individuals and depends on the severity of epilepsy”, the results of this study (and other similar studies) have often been misinterpreted. In particular, it has been often forgotten that selection criteria in this study excluded patients who were well controlled at lower concentrations. Separate studies have demonstrated that between 22% and 77% of unselected patients with recently diagnosed epilepsy achieve seizure control at phenytoin concentrations below 10 mg/L (Feldman and Pippenger 1976, Reynolds *et al.* 1981, Schmidt and Haenel 1984). This has led to the recommendation, regrettably not applied in many laboratories, that the lower limit of the “therapeutic range” of phenytoin (and all other AEDs) should be disregarded, and that any concentration greater than zero, up to the limit associated with a high probability of toxicity, should be regarded as potentially therapeutic (Perucca and Richens 1981, Perucca 2000).

These findings have important implications, because they question the practice, used by some physicians, of adjusting dosage to achieve serum drug levels within the quoted ranges during the first weeks of therapy. While this may be justified in selected cases, for example when for medical or psychosocial reasons it is imperative to minimize even a single seizure recurrence, in most cases the use of dosages larger than required may lead to unnecessary adverse effects (Woo *et al.* 1988), and in some patients, to the need to discontinue the initially prescribed AED with the attendant misdiagnosis of drug resistance. Similar considerations apply to the use of inappropriately large starting dosages or excessively fast titration rates (Kwan and Perucca 2005). For example, an idiosyncratic skin rash caused by too high an initial dose of phenytoin (Wilson *et al.* 1978) or lamotrigine (Messenheimer *et al.* 1998) may prevent subsequent use of these AEDs in a “refractory”

patient who might otherwise have responded well to the same AEDs.

Misconception 2: failure to increase dosage to the highest tolerated limit results in a high proportion of patients not achieving seizure control

It is often stated that in many patients with apparently refractory epilepsy, persistence of seizures frequently results from failure to increase AED dosage up to the highest tolerated level. In fact, there is little evidence that further dose increments in patients receiving dosages within the medium to high dose range results in seizure freedom in a large proportion of cases. In the observational UK study mentioned above, where dosage was “titrated to the limit of tolerability in patients still reporting seizures”, only 7% of patients who were seizure-free on carbamazepine required dosages above 800 mg daily, and only 8.5% and 16.5% of those controlled on valproate or lamotrigine, required dosages of these AEDs in excess of 1,500 mg and 200 mg per day respectively (Kwan and Brodie 2001). These results suggest that most patients who respond to initial monotherapy do so at low to moderate dosages, and that the gain derived from further increments in dosage is relatively modest. These observations should not be taken as an argument against the correct practice of increasing dosage up to the tolerability limit when seizures persist, but simply to challenge over-expectations about the impact of this practice in minimizing drug resistance.

Documenting that a single AED has been tried at the highest tolerated dose is important for long-term management, in order to avoid the situation where a physician may have to try a previously used AED again simply because of doubts that a sufficient dosage had been given. This situation is illustrated by a study of 74 consecutive patients referred for epilepsy surgery to a tertiary center in Germany because of “medical intractability” (Hermanns *et al.* 1996). None of these patients had ever been exposed to the highest tolerated dose of phenytoin, carbamazepine and phenobarbital or primidone. When one or more of these AEDs was increased up to the highest tolerated dose, no patient became seizure-free, but 7 patients (10%) reported a marked reduction in their seizures, which was considered sufficient to cancel their planned epilepsy surgery.

Misconception 3: knowledge of the mechanisms of action of an AED is not important for rational prescribing

The traditional approach to the treatment of epilepsy is empirical, AEDs being selected on the basis of their efficacy spectrum, tolerability profile, interaction potential

and ease of use (Beghi and Perucca 1995, Perucca 2001, National Institute of Clinical Excellence 2004, Sander 2004). In contrast with other therapeutic areas, *i.e.* hypertension or asthma therapy, mechanisms of drug action are not usually taken into consideration when choosing a medication for epilepsy. This is partly explained by the fact that the mechanisms responsible for seizure generation in an individual patient are still poorly understood, which prevents the application of mechanism-based therapy. Skepticism about the practical value of knowledge of modes of action of AEDs is reinforced by the observation that, historically, mechanism-driven drug development has had very limited success in epilepsy. Lamotrigine, for example, was designed as a potential anti-folate drug based on the hypothesis that such an action would be beneficial in preventing seizures (Peck 1994), and only later was it discovered that its effects relate to different mechanisms (*table 1*). Likewise, gabapentin was designed as a GABA agonist, only to discover in subsequent experiments that its seizure preventing activity does not primarily involve an action on the GABA system (Andrews and Fischer 1994, Stahl 2004). Topiramate, levetiracetam, oxcarbazepine, zonisamide and pregabalin were discovered by random screening or structural modification of pre-existing AEDs, rather than by mechanism-driven design. Ironically, the only two AEDs that were designed on a mechanistic basis, tiagabine and vigabatrin, are among those least widely used in current treatment.

While it is acknowledged that a fully mechanistic approach to the treatment of epilepsy cannot be proposed with the current state of knowledge, not least because modes of actions of AEDs are often multifactorial and incompletely understood (*table 1*), we cannot reject pharmacological mechanisms for rational prescribing entirely. To start with, information on mechanisms of action is useful for predicting the activity of AEDs against specific seizure types. In particular, AEDs which block voltage-dependent sodium channels, and AEDs which potentiate GABAergic transmission, have invariably been found to be effective against partial-onset seizures (Czapinski *et al.* 2005), whereas T-type calcium channel blockade appears to confer activity against absence and, possibly, myoclonic seizures (Van Lujtelaar *et al.* 2000). While other correlations are more difficult to establish, it seems to be a consistent observation that drugs that act by selectively increasing GABAergic activity, such as vigabatrin and tiagabine, have a potential for triggering or aggravating absence and myoclonic seizures, and have been implicated in the precipitation of non-convulsive status epilepticus, particularly in generalized epilepsies (Perucca *et al.* 1998). One of the greatest gaps in our knowledge is that we still lack a clear explanation as to why carbamazepine can precipitate absence and myoclonic seizures, particularly in patients with idiopathic generalized epilepsies (Genton *et al.* 2000). Possible hypotheses include syn-

Table 1. Main mechanisms of action of old and new generation AEDs.

	Blockade of voltage dependent sodium channels	Increase in brain or synaptic GABA levels	Selective potentiation of GABA-A mediated responses	Direct facilitation of chloride ion influx	Blockade of calcium channels	Other actions
Old generation AEDs						
Benzodiazepines	-	-	+	-	-	?
Carbamazepine	++	?	-	-	+ (L-type)	+
Ethosuximide	-	-	-	-	++ (T-type)	?
Phenobarbital	-	+	+	+	-	+
Phenytoin	++	?	-	-	?	+
Valproic acid	?	+	?	-	+ (T-type)	++
New generation AEDs						
Felbamate	++	+	+	-	+ (L-type)	+
Gabapentin	?	+	-	-	++ (N-, P/Q-type)	+
Lamotrigine	++	+	-	-	++ (N-, P/Q-, R-, T-type)	+
Levetiracetam	-	?	+	-	+ (N-type)	++
Oxcarbazepine	++	?	-	-	+ (N- and P-type)	+
Pregabalin	-	?	-	-	++ (N-, P/Q-type)	?
Tiagabine	-	++	-	-	-	+
Topiramate	++	+	+	-	+ (L-type)	+
Vigabatrin	-	++	-	-	-	+
Zonisamide	++	?	-	-	++ (N-, P-, T- type)	+

++ Primary action + Secondary action - No action described ? Controversial evidence or unknown.

Based partly on Perucca *et al.* (2001) and Czapinski *et al.* (2005).

chronization of the inactivation state of sodium channels (Osorio *et al.* 2000), and blockade of L-type calcium channels (Van Lujtelaar *et al.* 2000). An understanding of the mechanisms of action of AEDs may also provide working hypotheses with which to identify causes of unusual responses: for example, the observation that lamotrigine, a sodium channel blocker, often aggravates seizures in severe myoclonic epilepsy of infancy (Guerrini *et al.* 1998), may be explained by mutations of the gene encoding for the sodium channel SCN1A in patients with this disorder (Claes *et al.* 2001).

Knowledge of mechanisms of action are useful for predicting adverse effects. Although there are no entirely distinctive side effect profiles that clearly separate AEDs with different mechanisms of action, some adverse effects are more commonly associated with certain mechanisms. For example, weight gain, sedation and depressed mood appear to be associated more frequently with AEDs causing GABAergic potentiation (Marson *et al.* 1997); behavioural disturbances may be more prominent with NMDA receptor antagonists (Low *et al.* 2004). More importantly, specific adverse effects can be predicted by knowledge of ancillary pharmacological actions. For example, precipitation of hyponatremia by carbamazepine and oxcarbazepine can be anticipated from their known antidiuretic

activity (Wellington and Goa 2001), whereas inhibition of carbonic anhydrase by topiramate and zonisamide predicts the occurrence of side effects such as nephrolithiasis, paresthesias and metabolic acidosis (Inoue *et al.* 2000, Waugh and Goa 2003, Leppik *et al.* 2004, Groeper and McCann 2005).

An important consideration is whether mechanisms of action of AEDs should be considered in selecting the next drug in a patient who did not respond to existing treatment. Theoretically, when a first AED has failed, it would make sense to switch to a drug with a different mode of action, rather than to a drug sharing the same primary mechanism (Kwan and Brodie 2000b, Kwan and Brodie 2002, Beghi *et al.* 2003). Likewise, when combining two AEDs, greater benefit could be expected by adding a drug with a mode of action that is different, and potentially complementary, to that of the existing medication. Surprisingly, however, few studies have investigated systematically the effects of specific AED combinations. In a review that focused mainly on animal studies, Deckers *et al.* (2000) concluded that there is some evidence that (i) combining a sodium channel blocker with a drug enhancing GABAergic transmission can be advantageous; (ii) combining two GABAergic drugs or combining an AMPA antagonist with an NMDA antagonist may improve effi-

cacy but reduce tolerability; (iii) combining two sodium channel blockers is probably not advantageous. However, the authors were also careful to point out that adequate clinical trials on this issue have not been conducted, and that a mechanistic approach to combination therapy is currently unfeasible due to “incomplete knowledge of the pathophysiology of seizures and of the exact mechanisms of action of AEDs”. While this conclusion must be accepted, increasing clinical evidence does suggest that mechanisms of actions do influence the outcome of specific AED combinations (Perucca *et al.* 2002). In particular, the combinations of oxcarbazepine with carbamazepine (Barcs *et al.* 2000), and lamotrigine with carbamazepine (Besag *et al.* 1998, Messenheimer *et al.* 1998), have been associated with greater neurotoxicity compared with combinations of the same drugs with other agents. This may be explained by oxcarbazepine and lamotrigine sharing, with carbamazepine, a similar blocking action on voltage-dependent sodium channels, resulting in additive toxicity. Likewise, reports of a favourable pharmacodynamic interaction between lamotrigine and valproic acid have been explained by complementary modes of actions on different pharmacological targets (Brodie and Yuen 1997, Pisani *et al.* 1999, Cuadrado *et al.* 2002, Perucca and Levy 2002).

Misconception 4: there is no value in monitoring serum levels of new AEDs

There is widespread belief that monitoring serum levels of new AEDs has no value (Kilpatrick *et al.* 1996, Brodie 1998). This opinion is justified on the basis of studies that failed to identify clear-cut concentration ranges at which an optimal response is achieved (Kilpatrick *et al.* 1996, Neels *et al.* 2004). The claim that therapeutic drug monitoring (TDM) of new AEDs is not indicated is exploited as a promotional tool, because it is claimed that it simplifies management and reduces monitoring costs (Eadie 1998, Perucca 2000).

In fact, a critical review of the evidence does not support the statement that TDM of new AEDs is unlikely to be of value. Indeed, the reverse may be true, for a variety of reasons: (i) many new AEDs have a narrow therapeutic index, *i.e.* the dose required for seizure control is often close to that causing toxicity; (ii) there is a wide interindividual variability in the pharmacokinetics of these drugs; (iii) variability in pharmacokinetics and compliance contribute to a significant extent to differences in response; (iv) for some new AEDs, there is clearly a concentration threshold above which toxic effects are particularly common (Perucca 2000, Hirsch *et al.* 2004, Neel *et al.* 2004). These reasons are precisely those that provide a rationale for monitoring the blood levels of old generation AEDs. While it is true that a fixed range of therapeutic concentrations has not been defined for the newer AEDs, the same

can be said for the older AEDs, for which the concept of a fixed “therapeutic range” can be seriously criticised, as outlined earlier in this article.

The suggestion has been made that a modern approach to the use of serum AED levels should aim at identifying the optimal concentration at which each patient shows the best response. This can be done by adjusting dosage on purely clinical grounds, and measuring the concentration at which an optimal response has been achieved. Such measurements provide an “individualized reference concentration” that can be useful for subsequent management should intercurrent events (*e.g.* loss of compliance or a drug interaction) lead to seizure recurrence or onset of toxicity.

The “individualized reference concentration” concept can help clinical management. In a recent study, Specht *et al.* (2003) found that serum AED levels measured shortly after a breakthrough seizure in 52 patients treated mostly with carbamazepine, valproic acid and lamotrigine, were, in 44% of the cases, less than one-half the “individualized reference concentration” measured in each patient during periods of good seizure control. This was interpreted as evidence that in almost one half of the cases, seizure breakthrough was caused by non-compliance, a conclusion which could not be established without blood level monitoring. Another example of TDM contributing useful information comes from studies showing that serum lamotrigine levels decline markedly during pregnancy (Tomson *et al.* 1997, Ohman *et al.* 2000, Tran *et al.* 2002, De Haan *et al.* 2004, Pennell *et al.* 2004), or after starting the contraceptive pill (Sabers *et al.*, 2001, 2003, Sidhu *et al.* 2004), leading, in some cases, to deterioration of seizure control. Indeed, the long delay between the introduction of lamotrigine onto the market and the recognition of these important pharmacokinetic changes can be ascribed to the fact that TDM has not been widely practiced for this drug.

It should be pointed out that the applicability of the “individualized reference concentration” approach rests on the assumption that the relationship between serum AED concentration and response remains stable over time in the same patient. There are situations where concentration/response relationships may change over time, for example when there are changes in the underlying pathology, or when pharmacodynamic interactions occur with other drugs.

Misconception 5: successful surgery provides a cure for drug-resistant epilepsy

For some forms of refractory, localization-related epilepsy, resective surgery provides the best opportunity for seizure remission. The effectiveness of the surgical approach is unquestionable, and is supported by randomized controlled data (Wiebe *et al.* 2001). Although the probability

of success varies depending on the patient's characteristics, the surgical technique, assessment criteria and duration of follow-up, for temporal lobe surgery commonly quoted seizure freedom rates are in the order of 70 to 90% (Berg 2004). These figures are probably overoptimistic, because relapses are not uncommon during long-term follow-up (Schmidt *et al.* 2004a); in a recent study, 44% of patients who had been seizure-free one year post-surgery, relapsed during the 10-year follow-up (Yoon *et al.* 2003). Some of these relapses occurred despite ongoing AED therapy, while others were related to discontinuation of AEDs. If surgery is indeed curative, then continuation of AED treatment should not be required. On the other hand, at least in some patients, surgery may simply transform refractory epilepsy into a drug-responsive form. Differentiating between these possibilities is important, because it has implications for management (Schmidt and Löscher 2003). Unfortunately, no adequate studies have addressed this issue. A recent review of all relevant retrospective studies concluded that the risk of seizure recurrence in adults who underwent planned AED discontinuation after epilepsy surgery (mostly temporal lobe) stands at 34% over a follow-up of 1 to 5 years (Schmidt *et al.* 2004b). The risk of seizure recurrence after AED discontinuation may, however, be lower in children (Schmidt *et al.* 2004b). These data are not easy to interpret because late seizure recurrence after surgery is not uncommon even in patients who continue AED treatment (Schmidt and Löscher 2003, Yoon *et al.* 2003, Berg 2004), but they do suggest that in a subgroup of patients, seizure control remains dependent on continuation of pharmacological therapy. This interpretation seems to be reinforced by the observation that in the vast majority of patients who relapse, seizure control is regained following re-institution of AEDs. It is clear that we need more data to guide management practice in patients becoming seizure-free after surgery, and a randomized trial comparing AED taper with AED continuation is sorely needed.

Conclusions

Uncontrolled epilepsy entails a major burden in terms of human suffering and social costs, it being associated with increased mortality, mood disorders, other comorbidities, limitations in daily activities, psychosocial isolation and unemployment. Even in affluent societies, the dimension of the problem is of great concern. For example, in a recent UK study, about one half of 1,652 persons with epilepsy who participated in an epidemiological survey reported having had at least one seizure in the preceding year (Moran *et al.* 2004). While more effective AEDs are eagerly awaited to tackle the challenge of refractory epilepsy, at present the best way to minimize inadequate seizure control is to exploit at best available treatments. There are, at times, discrepancies between commonly

held opinions, and the body of scientific evidence that exists to support them. This article has discussed a number of relevant examples, and it is hoped that increased awareness of these issues could contribute, not only to an improved outcome, but also to high quality studies in many areas where gaps in knowledge prevent application of truly, evidence-based management. □

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