Recent advances in drug therapy for epilepsy

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Recent advances in drug therapy for epilepsy have contributed to the reduction in the proportion of persons whose epilepsy is uncontrolled. New knowledge of the pharmacokinetics of phenytoin has led to a better understanding of the drug's bioavailability and uses. Carbamazepine has recently been introduced for the treatment of generalized tonic-clonic and partial seizures. Clonazepam has been found of particular benefit in the treatment of absence and myoclonic seizures. Valproic acid is a promising antiepileptic drug with broad-spectrum activity, and is particularly useful in the treatment of absence and myoclonic seizures, although further clinical experience is required before it can supplant ethosuximide as the preferred drug for the treatment of absence seizures. Monitoring of the plasma concentration of antiepileptic drugs has added greatly to the achievement of optimal drug therapy and the prevention of toxic effects.

Les développements récents dans le traitement médicamenteux de l'épilepsie ont contribué à réduire la proportion des personnes dont l'épilepsie n'est pas contrôlée. Les nouvelles connaissances sur la pharmacocinétique de la phénytoïne a permis de mieux comprendre la biodisponibilité de ce médicament et ses emplois. La carbamazépine a récemment été introduite pour le traitement des crises d'épilepsie tonique-clonique généralisées et des crises d'épilepsie partielles. Le clonazépam a montré des avantages particuliers dans le traitement de l'absence et des crises myocloniques. L'acide valproïque est un antiépileptique prometteur ayant un large spectre d'activité, et il est particulièrement utile dans le traitement de l'absence et des crises myocloniques, bien que des études cliniques plus poussées soient nécessaires avant qu'il déclasse l'éthosuximide comme médicament de choix dans le traitement des crises d'absence. La surveillance des concentrations plasmatiques des médicaments antiépileptiques a grandement contribué à l'obtention d'un traitement médicamenteux optimal et à la prévention des effets toxiques.

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Recent advances in drug therapy for epilepsy have contributed to the reduction in the proportion of persons whose epilepsy is uncontrolled. New knowledge has been acquired about well established antiepileptic drugs such as phenytoin, and new antiepileptic drugs such as carbamazepine, clonazepam and valproic acid have been introduced. With increasing use of the newer agents it is important for primary care physicians to be aware of their limitations, therapeutic indications and possible toxicity. Potential interaction between antiepileptic drugs and other medications is another important consideration.[1,2]

With the drugs available today, significant seizure control can be achieved in 70% to 80% of persons with epilepsy, and complete control can be obtained in 60%.[3] Infantile spasms[4] and complex partial seizures[5] pose the most difficult therapeutic problems. Surgical procedures are most often used in individuals with temporal lobe epilepsy.[6]

The management of epilepsy is a dynamic process, and control of seizures may vary from time to time. Gradual and orderly changes in antiepileptic drug therapy are sometimes required. Successful management depends on the physician's ability to identify aggravating factors and knowledge of the use of antiepileptic drugs. The following review summarizes some recent advances that have added to our ability to successfully manage epilepsy.

Therapeutic agents

Phenytoin (Dilantin®)

Phenytoin remains the most studied antiepileptic drug. Its efficacy in the treatment of generalized convulsions, simple focal seizures and complex partial seizures (psychomotor seizures of the temporal lobe or the limbic system, or of insular origin) is well established.[7] More recently, new knowledge has been added about its bioavailability, use in pregnancy, interaction with other drugs and efficacy in the treatment of status epilepticus.

In daily doses of 4 to 7 mg/kg phenytoin is the most effective drug for the treatment of generalized tonic-clonic (grand mal) convulsions. It is also effective for the treatment of partial seizures. Since the drug is

well tolerated by most patients in single daily doses, compliance may be improved.[8] Children, however, should receive doses twice daily since they do not tolerate high doses well. Intramuscular administration is not recommended because of unpredictable and delayed absorption.[9-12] If oral or intravenous administration is not possible, intramuscular administration may be used, but the plasma concentration of the drug should be monitored. With the return to oral administration following intramuscular use, a lower oral dose should be given for a while to prevent a significant increase in the plasma concentration of the drug as a result of the delayed absorption from the intramuscular site.[13]

Intravenous administration of phenytoin is safe and effective in the treatment of grand mal status epilepticus.[14] Therapy can be initiated with a loading dose of 10 to 13 mg/kg given over 15 to 20 minutes to achieve satisfactory plasma concentrations more quickly. Possible cardiac toxic effects can be prevented by ensuring that the rate of administration does not exceed 50 mg/min. In a person with status epilepticus or frequent recurrent seizures a total dose of 10 to 13 mg/kg is recommended for maximal response. Phenytoin rarely produces respiratory depression. No significant effects on heart rate or blood pressure occur if rates of administration do not exceed those recommended.[14] A single dose of diazepam of 5 to 10 mg may be given simultaneously with phenytoin. Given intravenously diazepam may produce immediate cessation of seizures; however, a major antiepileptic drug is required to prevent recurrence of seizures.

Interaction of phenytoin with other drugs[1,2,15] may lead to increased total plasma phenytoin concentrations and possible dose-related toxic effects. The commonly used drugs with which such interaction can occur include disulfiram, isoniazid, bishydroxycoumarin, chloramphenicol, sulfonamides and benzodiazepines. In therapeutic doses salicylates and phenylbutazone, through their effects on protein binding, transiently increase the plasma concentration of free phenytoin. If high doses of salicylates are continued, increased clearance of the free drug may result in subsequent subtherapeutic concentrations of free phenytoin. Decreased total plasma phenytoin concentrations may result from concurrent administration of carbamazepine, ethanol or valproic acid. Drugs whose plasma concentrations are decreased by phenytoin administration include digitoxin, bishydroxycoumarin, contraceptive hormone preparations, doxycycline, dexamethasone, phenylbutazone, vitamin D, thyroxine and cortisol. Monitoring of the plasma phenytoin concentration is therefore stressed.

During pregnancy, decreased plasma phenytoin values despite a constant dose have been reported. In such circumstances the frequency of seizures may increase.[16,17] The plasma phenytoin values are then a useful guide to changing requirements for the drug. Changes in serum concentrations of electrolytes, hormonal status, nutritional status and drug biotransformation, as well as decreased phenytoin absorption, are possible factors.[18] Close supervision of the pregnant woman with epilepsy is required to prevent exacerbation of seizures and status epilepticus.

Carbamazepine (Tegretol®)

Carbamazepine was introduced in Europe as an antiepileptic drug in 1962. The drug is effective against generalized tonic-clonic seizures and partial seizures, including temporal lobe seizures. It is a major antiepileptic drug, not a supplemental medication.[19,20] Carbamazepine is rapidly absorbed from the gastrointestinal tract, with peak plasma concentrations occurring in 2 to 4 hours. It is 70% to 80% bound to plasma proteins. Since the plasma half-life is 12 to 14 hours, administration twice a day is required. Daily doses of 4 to 7 mg/kg (200 to 1600 mg) generally result in therapeutic plasma concentrations of 4 to 10 μg/mL. Patients receiving other antiepileptic drugs concurrently have lower plasma carbamazepine concentrations because of drug interaction.

Carbamazepine is excreted in the urine as carbamazepine epoxide and carbamazepine dihydroxide.[21,22] It is not clear whether the metabolites possess anticonvulsant properties.

Toxic symptoms due to carbamazepine include dose-related drowsiness, diplopia, ataxia, nausea and vomiting.[19] To minimize these side effects the initiation of therapy should be gradual. Impairment of hepatic and bone marrow function has been reported after long-term therapy. This may lead to aplastic anemia, agranulocytosis, thrombocytopenia and leukopenia.[23] Serial monitoring of hepatic function and hematologic variables is indicated, especially early in therapy. These adverse reactions, although potentially serious, are rare. Transient mild depression of the leukocyte count is frequent;[24] however, this often resolves without discontinuation of therapy. Carbamazepine has been a welcome addition to the treatment of generalized grand mal epilepsy, as well as of temporal lobe epilepsy, one of the most difficult varieties of seizures to treat. It may be used alone or in combination with other antiepileptic drugs.

Phenobarbital (Luminal®)

Phenobarbital is an effective major antiepileptic drug, used most commonly in combination with phenytoin in the treatment of tonic-clonic seizures and simple and complex partial seizures.[3] In children it may be used alone for these types of seizures. Phenobarbital is the preferred drug for the prevention and treatment of febrile seizures; however, its use for the routine prophylaxis of febrile seizures is controversial.[25-28]

Phenobarbital is completely absorbed from the gastrointestinal tract, reaching peak plasma concentrations after 4 to 7 hours. The drug is only 36% to 46% bound to plasma proteins.[29] Its plasma half-life ranges from 4 to 7 days. Daily doses of 1 to 5 mg/kg generally result in therapeutic plasma concentrations of 20 to 45 μg/mL.

Phenobarbital is predominantly metabolized by hepatic parahydroxylation and is partly excreted un-

changed in the urine.[30] Renal excretion can be enhanced by urinary alkalinization.

Toxic symptoms and signs include drowsiness, paradoxic excitation in children and elderly patients, nystagmus and ataxia. Rarely hepatic toxic effects, blood dyscrasias and hypersensitivity reactions occur.[31]

In adults a single daily dose is suitable. In a carefully controlled trial no difference in efficacy between primidone, phenobarbital and phenytoin was found in the treatment of complex partial seizures.[32] Comparisons of the efficacy of phenytoin and phenobarbital in the treatment of tonic-clonic seizures have produced conflicting results.[33-35]

Primidone (Mysoline®)

Primidone is an effective antiepileptic drug most commonly used alone or in combination with phenytoin in the treatment of complex partial seizures (psychomotor or temporal lobe seizures). It may also be used alone or in combination with phenytoin in the treatment of simple partial (focal) and generalized tonic-clonic seizures.

Primidone is rapidly absorbed from the gastrointestinal tract, with peak plasma concentrations occurring in 2 to 4 hours. Protein binding is negligible. The drug has a plasma half-life of 6 to 18 hours.[36] Daily doses of 10 to 25 mg/kg produce therapeutic plasma concentrations of 7 to 15 μg/mL.

Primidone is metabolized in the liver to phenylethylmalonamide and phenobarbital.[37] Both metabolites possess anticonvulsant properties, and phenobarbital ultimately accounts for 15% to 20% of the ingested primidone. After 2 to 3 weeks of primidone therapy, therapeutic plasma concentrations of phenobarbital are observed and can be used to monitor primidone therapy.

Adverse reactions to primidone similar to those observed with phenobarbital have been described.[38] The dose should be low when therapy is begun, then should be increased gradually to prevent gastrointestinal side effects. Since primidone is partly metabolized to phenobarbital, the two drugs should not be administered concurrently.

Clonazepam (Rivotril®, Clonopin®)

Clonazepam[39-43] is a benzodiazepine derivative of particular benefit in the treatment of absence (petit mal) seizures refractory to ethosuximide therapy. A specific indication for clonazepam is the Lennox-Gastaut syndrome, which is characterized by absence and myoclonic seizures. The drug is also useful for other types of seizures in which myoclonus is prominent. Daily doses of 1 to 20 mg produce average plasma therapeutic concentrations of 10 to 70 ng/mL. Clonazepam is rapidly absorbed and is 47% bound to plasma proteins; it has a plasma half-life of 22 to 38 hours. The initial daily dose in adults should be 0.05 mg/kg. Clonazepam is metabolized in the liver.

Toxic symptoms due to clonazepam include dose-related drowsiness, ataxia, irritability, depression and personality changes. Exacerbation of grand mal seizures occurs rarely with high doses. Sudden withdrawal may cause anxiety and irritability, and at times status epilepticus. It is a good general principle that when antiepileptic drug therapy is discontinued, the drug's dose should be decreased gradually.

Valproic acid (Depakene®)

Valproic acid and its sodium salt have recently been licensed in the United States for the treatment of absence seizures. The drug has broad-spectrum antiepileptic activity, being effective in the treatment of absence seizures, myoclonic seizures, generalized tonic-clonic seizures and, at times, partial seizures.[44-50] Valproic acid is a branched-chain carboxylic acid; in contrast to other antiepileptic drugs it lacks nitrogen and a ring moiety. Its mechanism of action is uncertain, but may be through its elevation of γ-aminobutyric acid concentrations in the brain.[51]

Valproic acid is rapidly absorbed from the gastrointestinal tract, with peak plasma concentrations occurring in 1 to 2 hours. It is 90% to 95% bound to plasma proteins and thus may displace phenytoin, which is 80% to 90% protein-bound.[48] It has a plasma half-life of 6 to 8 hours in most patients.[52] Daily doses of 10 to 50 mg/kg generally produce therapeutic plasma concentrations of 55 to 100 μg/mL.

Interaction between valproic acid and phenobarbital and phenytoin has to be considered if these drugs are used concurrently. Phenobarbital concentrations may rise during concurrent administration of valproic acid.[48,49] In a recent study of 25 patients 11 of the 13 receiving valproic acid concurrently with phenobarbital required a significant reduction of their phenobarbital dose.[49] Total plasma phenytoin concentrations were lower than expected in 10 of the 15 patients receiving valproic acid concurrently with phenytoin; however, only 3 required an increase in the daily phenytoin dose because of exacerbation of tonic-clonic seizures.[49] The displacement of phenytoin from protein-binding sites leads to a transient increase in free phenytoin and transiently enhanced metabolism of phenytoin by hydroxylating enzymes in the liver.

Therapeutic plasma concentrations can generally be achieved in 3 to 4 weeks.[50] Therapy should be initiated gradually: the daily dose should be 10 mg/kg in three divided doses at first and then should be increased at weekly intervals until seizure control is achieved or toxic symptoms develop.

Side effects are generally mild; however, hepatic function and hematologic variables should be monitored. Hepatotoxicity has occasionally been reported.[53] With initiation of therapy, nausea and vomiting may occur, but the problem is generally transient. Drowsiness may occur if the patient is concurrently receiving phenobarbital or primidone. Temporary hair loss, a mild tremor, weight gain, fatigue or mild thrombocytopenia may also occur. These side effects do not usually require discontinuation of therapy.

The indications for valproic acid therapy include absence seizures refractory to ethosuximide therapy, and myoclonic or tonic-clonic seizures refractory to therapy with phenytoin,

carbamazepine or phenobarbital, or a combination of these drugs. As further experience is acquired in the use of valproic acid, this drug may be found to be the preferred agent in patients who each have several types of seizures. Its efficacy in the treatment of absence seizures is equal to that of ethosuximide. It appears to be the preferred drug for the treatment of myoclonic seizures. Occasionally patients with temporal lobe seizures will respond to valproic acid therapy.

Monitoring of plasma concentrations

Monitoring of the plasma concentration of antiepileptic drugs is becoming part of the routine management of patients with epilepsy. The biologic activity of these drugs is proportional to their plasma concentration, and the plasma value is a better guide to antiepileptic effect than is the drug's dose. Such monitoring has contributed greatly to the prevention of consequences of adverse drug interactions in patients receiving multiple drug therapy. The plasma determinations are also useful in establishing patient compliance, in preventing dose-related toxic side effects and in achieving a "therapeutic range" for each patient to allow for differences in absorption, distribution, biotransformation and excretion of the drugs (Table I).

The indications for monitoring the plasma concentration of antiepileptic drugs can be summarized as follows:

1. At the initiation of therapy, to determine if the plasma concentration of the drug is satisfactory.
2. When seizures fail to be controlled or escape from control, to help determine whether poor patient compliance, rapid drug metabolism or resistance to the drug is the responsible factor.
3. When the dose of the drug is changed and a new steady state is achieved.
4. When toxic symptoms occur that may be drug-related.
5. When another drug is added to the regimen that might lead to an undesirable drug interaction.
6. During an intercurrent illness, such as gastrointestinal, hepatic or renal disease, that might interfere with absorption, biotransformation or excretion of the drug.
7. During pregnancy, when alterations in absorption and metabolism of the drug may occur, necessitating an adjustment of dosage.[18]
8. During antiepileptic drug research trials.

The concept of a therapeutic range is statistical. It represents the range of plasma drug concentrations associated with optimal seizure control in most patients without the production of unacceptable adverse side effects. In some patients optimal control is achieved with subtherapeutic plasma concentrations; these patients should not have their dose increased. In some patients toxic adverse effects occur with subtherapeutic or therapeutic concentrations; if these side effects are unacceptable, the dose of the drug will have to be reduced or another drug given in its place.

Drug assays done by most laboratories measure the plasma concentration of the total (bound plus unbound) and not the free (unbound) drug. This limitation has to be recognized since it is only the free drug that can act at the drug's site of action. Also, efficacy and toxicity correlate better with the free drug concentration than with the total drug concentration.[54] Particular care must be taken in treating patients who have hepatic disease or uremia with antiepileptic drugs. Hepatic disease may lead to a decrease in plasma protein binding and a change in metabolism.[55] In uremia the renal excretion of phenobarbital and phenytoin metabolites may be impaired, and low plasma protein concentrations could lead to increased plasma concentrations of free phenytoin.[56,57] The result of drug interaction at protein binding sites is unpredictable, and depends in part on whether a drug has restrictive or nonrestrictive elimination. Only monitoring of each drug's plasma concentration can give some insight into the significance of an interaction.

The optimal potential of antiepileptic drug monitoring has not yet been achieved. More significance will be derived from plasma values when laboratories are able routinely to measure free drug concentrations. The possibility of measuring the salivary concentration of an antiepileptic drug as an indication of the plasma concentration of free drug is being investigated.[58-60] With an understanding of the limitations of plasma monitoring, however, the proportion of persons whose epilepsy is uncontrolled and the frequency of dose-related adverse reactions can be reduced. This technique is an additional way for the clinician to obtain maximal benefits from all drugs being used.[49,50,61-65]

Table I—Therapeutic plasma concentrations of antiepileptic drugs

Drug	Therapeutic range†	Usual daily dose (mg/kg)	Time to reach steady state (days)
Phenytoin	10–20 μg/mL	4–7	7–9
Carbamazepine	4–10 μg/mL	7–15	3–4
Phenobarbital	20–45 μg/mL	1–5	14–21
Primidone*	7–15 μg/mL	10–25	4–7
Clonazepam	10–70 ng/mL	0.1–0.2	Unknown
Valproic acid	50–100 μg/mL	10–60	4
Ethosuximide	40–100 μg/mL	20–30	7–10

*Primidone's two metabolites, phenobarbital and phenylethylmalonamide, have antiepileptic properties. Primidone therapy can be monitored by the plasma concentrations of phenobarbital.
†Source of data: epilepsy research laboratory, Epilepsy Research Foundation of Florida.

Conclusions

Phenytoin remains the main antiepileptic drug for the treatment of generalized tonic-clonic seizures, although carbamazepine, primidone and phenobarbital are also effective. If a single drug in therapeutic doses does not control the seizures, a combination of phenytoin and carbamazepine, phenobarbital or primidone may be tried. Treatment of the various types of seizures is summarized in Table II.

For the treatment of absence seizures, ethosuximide is the preferred drug. Valproic acid is just as efficient as ethosuximide, but more clinical experience is required with the use of the former. In patients with absence seizures who have a history of grand mal seizures, phenytoin should be administered concurrently. Valproic acid has broad-spectrum activity, and in the future may prove to be the preferred drug for patients with several types of seizures. Trimethadione is effective against absence seizures; however, because of potentially serious hematopoietic depression, hepatitis and nephrosis, it should not be used to initiate treatment. Clonazepam may be of benefit in some patients whose condition is refractory to therapy with other drugs.

For the treatment of myoclonic seizures valproic acid is highly efficient, and some consider it the preferred drug.[46] Benzodiazepines may prove effective in some cases.

For the treatment of complex partial seizures phenytoin, carbamazepine or primidone may be effective alone. Phenytoin or primidone may be combined with carbamazepine, and phenytoin may be combined with primidone. Occasionally a combination of all three is required.

For the treatment of grand mal status epilepticus diazepam may be given intravenously for immediate control and in combination with phenytoin for prolonged control.

Failure of antiepileptic drug therapy is most often due to poor patient compliance, inadequate dosage, use of an inappropriate drug or combination of drugs, incorrect diagnosis, progressive neurologic disease or, rarely, drug toxicity.

Table II—Treatment of various types of seizures

Seizure type	Drugs*
Tonic-clonic (grand mal)	Phenytoin Carbamazepine Phenobarbital Primidone Valproic acid
Simple or complex partial (focal)	Phenytoin or carbamazepine Primidone Phenobarbital Valproic acid
Absence (petit mal)	Ethosuximide Valproic acid Clonazepam Trimethadione
Myoclonus	Valproic acid Clonazepam Nitrazepam

*Listed in order of decreasing preference; drugs may be used in combination.

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