Adverse effects of antiepileptic drugs in children

The relevance of drug interaction

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THERE is a growing concern that multiple antiepileptic drug therapy is a major cause of unnecessary and avoidable drug toxicity. This short overview will summarize recent data on adverse effects in children induced by multiple antiepileptic drug therapy and interactions of antiepileptic drugs. Attention is directed to those interactions which lead to clinical drug toxicity and require dosage reduction. For a systematic review of adverse effects the interested reader is referred to recent publications.[1,2]

MECHANISMS OF ANTIEPILEPTIC DRUG INTERACTIONS

The majority of these interactions manifest themselves in changes of the pharmacokinetic parameters of the antiepileptic drug or the other drug(s). Interactions involving pharmacodynamic parameters have less often been implicated in various drug combinations.

Pharmacokinetic interactions usually become evident when signs of antiepileptic drug intoxication appear in patients receiving recommended dosages of antiepileptic drugs during a combination treatment or in combination with recommended dosages of other drugs. The critical period for these interactions is usually the first few weeks or months of drug administration.

Mechanisms involved in pharmacokinetic interactions vary. They include pharmacologic interactions such as intoxication in Australian patients whose phenytoin plasma concentrations increased when the filler was changed from calcium to lactose.[3]

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Inhibition of biotransformation of the parent drug or its metabolite is by far the most common interaction, leading to accumulation of the parent drug or the active metabolite. Induction may less often lead to toxicity through an increase in toxic metabolites. Drug toxicity may also result from disinduction when an enzyme-inducing drug is withdrawn from a drug combination with subsequent increase of the plasma concentration of the remaining agent.

Phenytoin, valproic acid and benzodiazepines such as clonazepam, clobazam and diazepam bind to a high degree to plasma protein. When highly bound drugs are used in combination, interactions may occur, resulting in increased free fraction in the plasma concentration and increased elimination and binding into tissues. At steady state, the overall result of the interaction is a lower total plasma concentration and an unchanged free concentration. The situation becomes more complex if the displacing agent (e.g., valproic acid) is also an inhibitor of the biotransformation of the drug or its metabolite. If this is the case, adverse effects may occur at a relatively low total and unchanged plasma concentration because the free concentration increases.[4]

The same drug in combination with an antiepileptic drug may not have the same effect in all patients. Dosage and duration of treatment with the other drug, as well as genetic and environmental factors, cause variable individual susceptibility.[5]

INTERACTIONS OF ANTIEPILEPTIC DRUGS WITH OTHER DRUGS

A number of reported interactions are of special interest for the treatment of children, e.g., the interaction of antiepileptic drugs with analgesics and anti-

TABLE 1
TOXICITY-CAUSING DRUG COMBINATIONS

Antiepileptic drugs	Other drugs
Phenytoin	Amiodarone
Phenytoin	Chloramphenicol
Phenytoin	Chlordiazepoxide
Phenytoin	Chlorpheniramine
Phenytoin	Chlorpromazine
Carbamazepine, phenytoin	Cimetidine
Phenytoin	Disulfiram
Carbamazepine	Erythromycin
Phenytoin	Imipramine
Carbamazepine, phenytoin, primidone, diazepam, ethosuximide	Isoniazid
Carbamazepine	Lithium
Phenytoin	Miconazole
Carbamazepine, primidone	Nicotinamide
Phenytoin	Phenylbutazone
Phenytoin	Prochlorperazine
Carbamazepine, phenobarbital, phenytoin	Propoxyphene
Phenytoin	Sulfonamides
Phenobarbital, phenytoin	Thioridazine
Phenytoin	Trazodone
Carbamazepine	Triacetyloleandomycin

The majority of these interactions lead to higher plasma concentrations of the antiepileptic drug. Interactions involving pharmacodynamic parameters have been assumed in some drug combinations (e.g., lithium and carbamazepine). Variable individual susceptibility exists. For a more detailed review see reference 5.

TABLE 2
MEDICATIONS WHICH HAVE CLINICALLY RELEVANT INTERACTIONS WITH ANTIEPILEPTIC DRUGS

Acetaminophen
Bishydroxycoumarin
Chloramphenicol
Chlorpromazine
Cimetidine
Cyclosporine
Dexamethasone
Digitoxin
Doxycycline
Folic acid
Furosemide
Griseofulvin
Haloperidol
Meperidine
Methadone
Nortriptyline
Oral contraceptives
Quinidine
Theophylline
Vitamin D
Warfarin

These drugs are influenced by phenytoin, phenobarbital or carbamazepine. The interaction often leads to a reduced effectiveness of the drug and frequently requires increased dosages.

pyretics such as propoxyphene and phenylbutazone, or antibiotics or antimicrobial agents such as sulfonamides and isoniazid (*Table 1*).

Methylphenidate has caused a rise in plasma phenytoin concentration in a few patients.[5] In one child receiving primidone, methylphenidate was found to increase both the primidone and the phenobarbital plasma concentrations, but has had no such effect in others.[6]

Clinical interactions in which the kinetics of other drugs are altered by antiepileptic drugs may be of relevance, and are seen as an indirect adverse effect of antiepileptic drug therapy (*Table 2*).

Among antipyretic agents, acetaminophen metabolism is induced by phenobarbital, leading to an increase of a toxic product. The epileptic child might be at higher risk in case of acetaminophen overdose.[7] Asthmatic children receiving phenytoin, phenobarbital or carbamazepine may need higher and more frequent doses of theophylline because the plasma clearance of theophylline is increased by 20% to 50%.[8] The metabolism of antimicrobial agents such as griseofulvin, doxycycline and chloramphenicol; of anticoagulants such as cimetidine and furosemide; and of cardiac drugs such as quinidine and digitoxin is increased in patients receiving phenytoin, phenobarbital or carbamazepine.[5]

The reduced maximal concentration of cyclosporine in children receiving phenytoin, phenobarbital or carbamazepine is of special relevance. Addition of phenobarbital markedly reduced the plasma concentration and the desired clinical effects of cyclosporine in a 4-year-old child.[9] Conversely, experimental cyclosporine nephrotoxicity was reduced in animals treated with phenobarbital.[10] The mechanism in these interactions was thought to be induction of cyclosporine metabolism. Recent data suggest that phenytoin reduces absorption of cyclosporine. Rowland and Gupta, however, did not find evidence that phenytoin induces cyclosporine metabolism.[11] Valproic acid is preferable to carbamazepine or other enzyme-inducing antiepileptic drugs in patients with epilepsy receiving cyclosporine following renal transplantation (*Figure 1*).[12]

The metabolism of steroids, e.g. oral contraceptives and dexamethasone, is induced considerably by phenytoin, phenobarbital or carbamazepine. Reduced effectiveness of prednisone and prednisolone has been described in those receiving antiepileptic drugs.[13]

Interactions have long been noted between vitamin D and antiepileptic drugs. Osteomalacia related to the deficiency of vitamin D has occurred in some epileptic children. Low plasma concentrations of 25-hydroxy

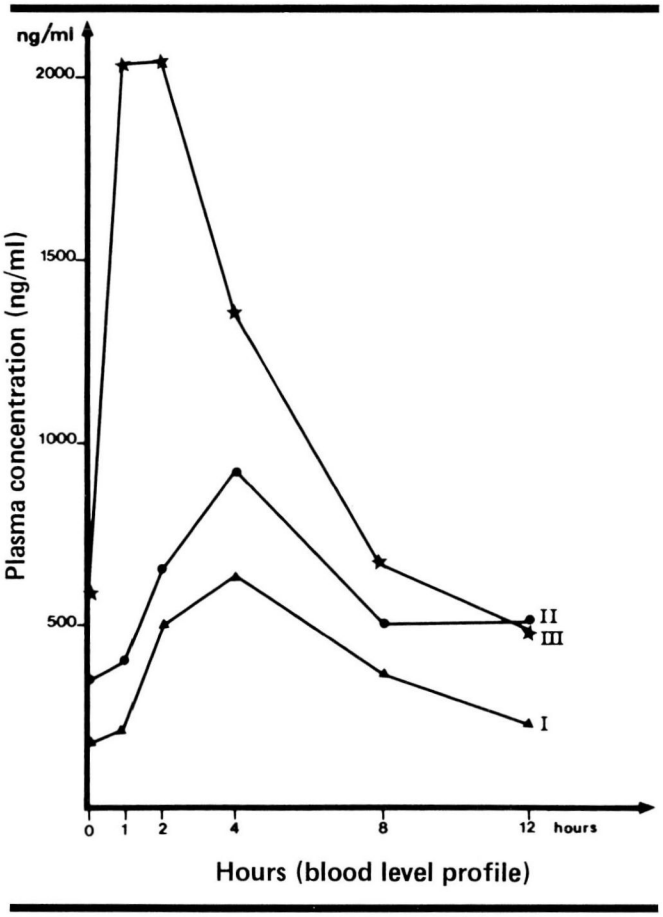

FIGURE 1. Replacement of carbamazepine by valproic acid leads to an increase of cyclosporin blood levels in one patient with a constant dosage of 10 mg/mL body weight of cyclosporin. Valproic acid is preferable to carbamazepine or other enzyme-inducing antiepileptic drugs in patients with epilepsy receiving cyclosporin following renal transplantation.[12] (I=before, II=one week after, and III=four weeks after replacement of carbamazepine by valproic acid)

cholecalciferol, the active metabolite of vitamin D, are usually seen in these children. Although the mechanism producing osteomalacia appears to be incompletely understood, induction of microsomal enzymes is implicated, possibly through the increased production of inactive metabolites.[5] Environmental factors such as the amount of sunlight and the content of vitamins in the diet seem to determine which patients develop clinical osteomalacia. Treatment of symptomatic patients is usually 4,000 units of vitamin D daily. In a recent study, vitamin D2 was found primarily to increase the bone mass, while D3 decreased calcium excretion in patients treated with 4,000 units daily.[14] For children taking antiepileptic drugs, prophylactic treatment with vitamin D is generally not recommended.

TABLE 3
FREQUENCY OF ADVERSE EFFECTS OF ANTIEPILEPTIC DRUGS DURING TRIALS WITH SINGLE- OR MULTIPLE-DRUG THERAPY

	Single-drug therapy %	Multiple-drug therapy %
Carbamazepine	33	47
Phenobarbital	38	55
Phenytoin	38	50
Primidone	20	35
Valproate	25	35
Methosuximide	25	50
Ethosuximide	16	18
Mephenytoin	17	17
Average	27	38

For most antiepileptic drugs, adverse effects are more frequent during multiple-drug therapy with the exception of ethosuximide and mephenytoin, which are less often involved in drug interactions.

INTERACTIONS DURING MULTIPLE ANTIEPILEPTIC DRUG THERAPY

It has been estimated that 40% to 50% of patients with epilepsy receive combinations of more than one antiepileptic drug. Adverse effects are more frequent during multiple-drug therapy except for drugs like ethosuximide, which seldom interacts with other drugs (*Table 3*).

Valproic acid

The addition of valproic acid to phenytoin treatment has resulted in phenytoin drug toxicity. A recent example was given by Wilder (Wilder J. Personal Communication, 1988). A child who received phenytoin and had a total phenytoin plasma concentration of 10 μg/mL and a free concentration of 1 μg/mL received 500 mg valproic acid and complained about diplopia and ataxia 45 minutes later. The total plasma concentration of phenytoin again was 10 μg/mL; the free concentration, however, had risen to 3.1 μg/mL, explaining the phenytoin drug toxicity. The mechanism of this drug interaction is complex. The rise in the free plasma concentration is suggestive of displacement and inhibition of phenytoin biotransformation. Valproic acid displaces benzodiazepines from protein binding and increases the free concentration of diazepam or

clobazam in plasma. This interaction may provide an explanation for the occasional observation that the sedative effects of benzodiazepines (e.g., clobazam) are potentiated by concurrent medication with valproic acid.

When valproic acid is added to carbamazepine, an interesting interaction can be observed. Valproic acid leads to an increase in the plasma concentration of the 10,11-epoxide of carbamazepine.[15] Recently Meijer et al have shown that the amide of valproic acid has an even more pronounced effect.[16] When valpromide was substituted for valproate, carbamazepine 10,11-epoxide increased from 2.1 to 8.5 μg/mL, while carbamazepine remained at 6.9 and 6.8 μg/mL respectively. The mechanism of this interaction has been elucidated recently.

Valproic acid and, to an even greater extent, valpromide are inhibitors of epoxide hydroxylase, which metabolizes the carbamazepine 10,11-epoxide.

In five of seven patients, this interaction has led to clinical intoxication with 10,11-epoxide, which produced clinical side effects similar to those of carbamazepine, even though the drug did not increase its serum concentration. Lindhout et al[17] have presented data showing that the rate of teratogenicity in the offspring of epileptic mothers was higher when they received a combination of carbamazepine with valproate, phenytoin and phenobarbital. These investigators have also shown that the epoxide is highest in patients receiving carbamazepine together with valproate, phenytoin and phenobarbital. They have suggested that the formation of epoxides or related compounds might be of relevance to the teratogenic effect of carbamazepine combinations. The relevance of these speculations is difficult to evaluate, as the authors seem to imply that the stable 10,11-epoxide has teratogenic potential similar to that of free radical drug epoxides, which have been the object of concern for their potential teratogenicity in other areas. Currently there is no evidence, however, that the stable carbamazepine 10,11-epoxide has teratogenic properties. The observed interaction would strongly support single-drug therapy during pregnancy.

Carbamazepine

The plasma concentrations of carbamazepine and its epoxide and other active metabolites are influenced by other antiepileptic drugs. The plasma concentration of carbamazepine is lower when phenytoin, primidone, phenobarbital or valproate are added. The plasma concentration of carbamazepine epoxide, however, is increased by valproate (+45%), by primidone (+19%) and by their combination.[15] The clinical result of this interaction is toxicity with higher concentrations of the epoxide in plasma. Carbamazepine epoxide has been shown to have antineuralgic effects[18] as well as antiepileptic effects. The relevance of carbamazepine 10,11-epoxide for side effects is currently not well known. Lateral-gaze nystagmus has been studied in patients receiving carbamazepine alone, and in those receiving phenobarbital and carbamazepine. Nystagmus was observed in 26% of those receiving carbamazepine alone, and in 33% of those receiving carbamazepine and phenobarbital. No evidence was found in this study of a role for carbamazepine epoxide, even though nystagmus tended to develop at lower carbamazepine concentrations in patients taking both phenobarbital and carbamazepine than in those taking carbamazepine alone.[19] This could be explained through a pharmacodynamic interaction. Phenobarbital itself can induce nystagmus, especially at high concentrations.[1] Recent data have shown, however, that the epoxide may be responsible for the development of toxicity when valproate is added to carbamazepine.[16]

Phenytoin

Phenytoin metabolism is particularly vulnerable to inhibition by other drugs since its parahydroxylation is a saturable process. Sulthiame, a sulfonamide with carbonic anhydrase inhibitory properties, is a powerful inhibitor of phenytoin and phenobarbital metabolism. Methsuximide has been reported to cause an elevation in the serum concentration of phenytoin and phenobarbital.[4] When carbamazepine is added to phenytoin, an elevation of phenytoin plasma concentration of 36% may occur, giving rise to drug toxicity in 20% of patients.[20] However, this study was retrospective, and others have reported that this interaction is highly variable.

ADVERSE EFFECTS DURING MULTIPLE-DRUG THERAPY

The toxicity of antiepileptic drugs is often difficult to evaluate. In many cases, the dosage of the first drug has been reduced by the physician before or while the second drug is added. This procedure is often not clearly outlined in the methods section of reports dealing with two-drug therapy. If the dosage of the first drug has been lowered, the toxicity of receiving two drugs will be underestimated. In addition, the dosage of the second drug may be increased, if necessary, until

TABLE 4
RESULTS IN PATIENTS TRANSFERRED FROM TWO-DRUG THERAPY TO SINGLE-DRUG THERAPY

	Two-drug therapy	Single-drug therapy
Number of patients	63	63
Number of patients with seizure reduction (75% or more)	0	6
Median seizure frequency	1.3	1.2*
Total number of patients with side effects	32	29
Number of patients with side effects during both drug regimens	22	22 (3)
Number of patients who developed side effects during transfer	0	7 (2)
Number of patients in whom side effects disappeared during transfer	10	0 (1)

During transfer from two-drug therapy to single-drug therapy in patients with uncontrolled partial epilepsy, an effort was made to increase the plasma concentration of the remaining drug for maximum efficacy if necessary until clinical drug toxicity prevented a further increase. Note that six of 63 patients had fewer seizures; however, the median seizure frequency was not significantly lower during single-drug therapy. Even though ten patients had lost their side effects when transferred to single-drug therapy, seven patients required an increase of dosage during single-drug therapy, leading to new side effects. The net result is a similar number of patients with side effects (32 vs 29) in both regimens. The numbers of patients who benefited from single-drug therapy are given in parentheses and are broken up into three subgroups: three patients continued to have side effects, two patients had side effects which disappeared, and one developed side effects while receiving only one drug.

TABLE 5
RESULTS IN PATIENTS WHO HAD ADDITION OF A SECOND DRUG

	Single-drug therapy	Two-drug therapy
Number of patients	68	68
Number of patients with seizure reduction (75% or more)	0	15
Median seizure frequency per month	2.3	1.3*
Total number of patients with side effects	42	39
Number of patients with side effects during both drug regimens	26	26 (5)
Number of patients in whom side effects disappeared during transfer	16	0 (6)
Number of patients who developed side effects during transfer	0	13 (4)

Adding a second drug in patients with disease uncontrolled by single-drug therapy with primary antiepileptic drugs (carbamazepine, phenytoin, phenobarbital or primidone) resulted in a seizure reduction of 75% or more in 15 of 68 patients. The second drug again was one of the primary antiepileptic drugs described above.
Side effects were introduced by the addition of a second drug in 13 patients, while 16 patients had side effects only during single-drug therapy, the net result being that the number of patients with side effects remained similar. The numbers of patients who benefited from two-drug therapy are given in parentheses and broken up into three groups: 5 patients continued to have side effects during two-drug therapy, 6 patients lost their side effects, and 4 patients developed side effects during two-drug therapy.
* $P = 0.015$

complete seizure control develops or drug toxicity prevents a further dosage increment. As a result, the patient with intractable epilepsy may suffer from drug toxicity during single-drug therapy as well as during two-drug therapy. It is, therefore, rather difficult to evaluate the contribution of the second drug to the toxicity (*Tables 4* and *5*).

Another facet of multiple-drug therapy is the poor risk-benefit ratio revealed when the antiepileptic efficacy of drug combinations is critically assessed. Recent studies in newly diagnosed and in chronic epilepsy have convincingly illustrated the limited efficacy of adding a second antiepileptic drug. In partial epilepsy, about 11% to 22% of patients have more than a 75% seizure reduction when a second drug of first choice (i.e., carbamazepine, phenytoin, phenobarbital or primidone) is added. This applies to patients who did not become seizure-free despite maximum tolerable plasma concentrations of a drug of first choice during single-drug therapy.[21,22]

In some patients, transfer to single-drug therapy is associated with a decrease in seizure frequency. According to a recent study, 83% of patients with partial seizures uncontrolled by two antiepileptic drugs had fewer seizures or as many seizures when they were transferred to single-drug therapy.[23] In patients with Lennox-Gastaut syndrome, decreased alertness resulting from high dosages of several antiepileptic drugs led to an increased incidence of seizures (*Figure 2*).[24] Exacerbation of seizures, especially tonic seizures, has been described during addition of benzodiazepines in patients with Lennox-Gastaut syndrome. This observation raises the intriguing question of exacerbation of seizures by antiepileptic drugs.[25] Carbamazepine has recently been considered a possible precipitating factor in a child with an increased seizure frequency of generalized tonic-clonic seizures and absence seizures.[26] This limited study cannot reasonably exclude a fluctuation of the course of epilepsy unrelated to drug exposure. Carbamazepine has also been implicated in

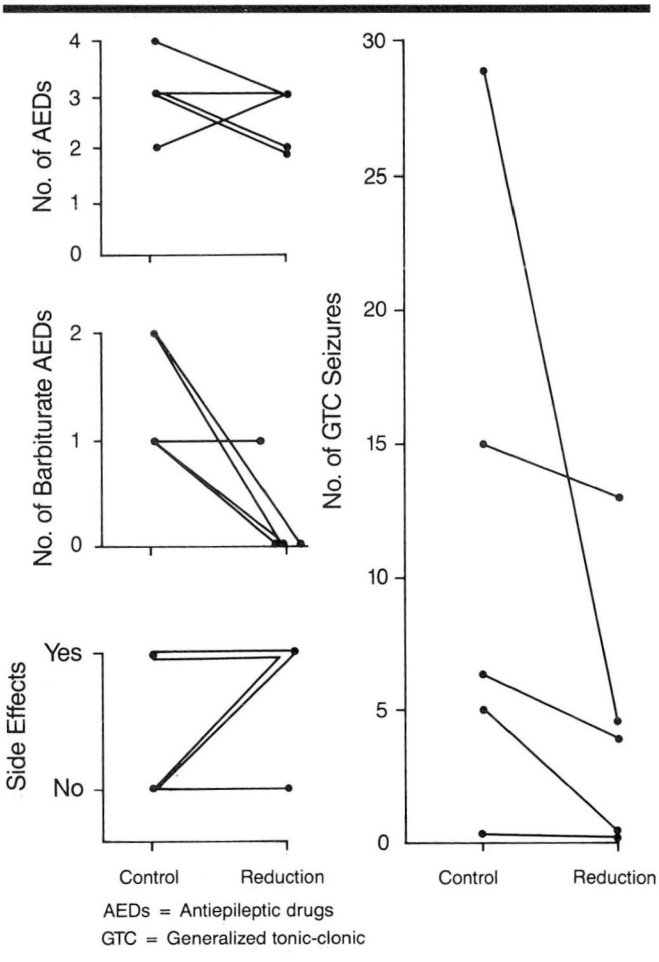

FIGURE 2. Reduction of polypharmacy in five patients with Lennox-Gastaut syndrome. The number of barbiturate antiepileptic drugs, e.g., phenobarbital and primidone, was reduced by 50 mg and 250 mg per month respectively. The daily dose of the remaining drugs, phenytoin or carbamazepine, was increased until complete seizure control was achieved or clinical tolerance precluded any further dose increment. Seizure control improved while side effects were not markedly reduced during reduction of polypharmacy (modified from Schimdt and Machus, 1980[25]).

inducing nonepileptic myoclonus in a child with benign epilepsy, raising the possibility that myoclonus may be misdiagnosed as epileptic seizures. Finally, an increase of absence seizures has been associated with the introduction of sedative agents such as phenobarbital, and more recently of gamma aminobutyric acid (GABA)-ergic agents such as progabide, in previously untreated patients with absence seizures.[27] This latter clinical observation correlates well with experimental evidence that GABA agonists have epileptogenic potential in animal models of seizures.[28]

TABLE 6
PREVENTION OF ADVERSE EFFECTS

1. Early adequate treatment
2. Appropriate drug choice
3. Single-drug therapy
4. Drug monitoring
5. Avoidance of acute toxicity
6. Determination of lowest effective plasma concentration
7. Avoidance of add-on therapy, if possible
8. Transfer to single-drug therapy in uncontrolled epilepsy, if possible
9. Increased awareness of toxicity

Prevention of side effects includes a number of principles which are applied with a degree of flexibility to individual cases. Overemphasis on multiple-drug therapy or high-dose therapy (even when it cannot control seizures) is a major cause of adverse effects.

PREVENTION OF ADVERSE EFFECTS

From a clinical perspective, adding a second drug is recommended only when the first drug has failed in a maximum tolerable daily dosage. Reliance on published therapeutic ranges of plasma concentrations is not useful because the plasma concentration required for complete seizure control varies considerably from patient to patient. For example, therapeutic plasma concentrations are higher in patients with partial seizures than in those with generalized tonic-clonic seizures.[29] In addition, great individual differences exist with regard to the plasma concentration at which clinical drug toxicity appears.[30] During phenytoin single-drug therapy, plasma concentrations of as low as 7 mg/mL and in rare cases as high as 49 mg/mL were associated with lateral-gaze nystagmus and ataxia. About 25% of patients in this study developed drug toxicity at plasma concentrations of below 20 mg/mL, which is usually quoted as the upper end of the safe therapeutic range.[1] Plasma concentrations of 33 mg/mL or more are a reasonable estimate of the point at which to expect side effects in most patients receiving phenytoin.

No confirmation in experimental studies has been found for the theory that two-drug therapy will result in less toxicity because the side effects of the two drugs may differ and be infra-additive, while their antiepileptic effects are in fact additive or even supra-additive.[31] Quite to the contrary, alternative single-drug therapy seems to be promising when single-drug therapy has failed. Alternative single-drug therapy resulted in sei-

zure reduction of 75% or more in 31% of patients refractory to previous single-drug therapy.[32] Gradual transfer to single-drug therapy is beneficial for most patients. In patients who have become seizure-free upon addition of the second drug, the first drug may not be required for seizure control. In patients who continue to have seizures, pharmacokinetic interaction may hinder the plasma concentration of the second drug from increasing and becoming more effective.

The success of transfer to single-drug therapy as a means of controlling adverse effects is difficult to judge because the remaining drug is usually increased to maximum tolerable daily dosage for optimal seizure protection (*Tables* 4 and 5). If it has been shown that seizure control cannot be achieved by high dosages of one or two primary antiepileptic drugs, sound clinical judgment implies that it is best to find out if the daily dosage can be reduced. Slow reduction of the daily dosage will result in fewer side effects, and can be tolerated without an undue increase in seizures in most patients. If the patient is not a surgical candidate, a low-risk regimen of (preferably) a single drug at the lowest effective dosage is the optimal choice until better antiepileptic drugs become available (*Table* 6).

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