Medical therapy for intractable complex partial seizures[1]

Harold H. Morris III, M.D.
Ronald P. Lesser, M.D.
Hans Lüders, M.D., Ph.D.
Dudley S. Dinner, M.D.

Treatment of intractable complex partial seizures should reduce the frequency or severity of the attacks and reduce or eliminiate side effects from the medication. Most important, a correct diagnosis of seizure type should be attained. Frequently, an evaluation and subsequent treatment changes can best be carried out if the patient is hospitalized. The advantages of high-dose monotherapy with phenytoin, carbamazepine, or primidone are discussed. The effectiveness and methodology of the secondary anticonvulsants (benzodiazepines, valproic acid, methosuximide, acetazolamide, and progestational agents) are reviewed. Many patients can be treated with one nonsedating anticonvulsant.

Index words: Anticonvulsants • Epilepsy, temporal lobe • Seizures

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Intractable seizures are epileptic attacks which continue despite therapy with appropriate anticonvulsants. The goals of treatment are twofold: to completely control the seizures or, if this is impossible, to reduce their frequency and reduce or eliminate the side effects from the anticonvulsants employed.

Diagnosis

Evaluation and treatment of most patients with intractable complex partial seizures ideally should be done initially in the hospital. The importance of hospitalization and intensive monitoring has been demonstrated clearly by Porter et al[1] and Theodore et al.[2] In the latter study, hospitalization facilitated evaluation and a subsequent

[1] Department of Neurology, The Cleveland Clinic Foundation. Submitted for publication and accepted Oct 1983.

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change in the diagnosis of seizure type in 22 of 74 cases. The most common errors were classifying complex partial seizures as absence seizures or classifying absence or psychogenic seizures as complex partial seizures. A changed diagnosis, in turn, led to more effective treatment and an improved prognosis. Porter et al[1] studied 23 patients with intractable epilepsy and, after in-hospital monitoring and adjustment of medications, were able to improve seizure control in 70% and reduce toxicity in 83%. According to Riley et al,[3] however, hospitalization may result in decreased seizure frequency even without medication changes.

Therapy

Monotherapy vs. polytherapy

The type and combination of drugs used for treatment are also important considerations. In a recent paper, Theodore and Porter[4] reported their findings after withdrawing all barbiturates and benzodiazepines from the drug regimen of 78 patients with intractable seizures. The patients were given only nonsedating anticonvulsants. After six months, adverse drug-induced side effects lessened and seizure control improved in 51%, only drug-induced side effects lessened in 19%, and only seizure control improved in 12%. The condition of 16% was unchanged. The condition of 1 patient became worse. The authors concluded that sedative anticonvulsants were not necessary for optimal seizure control of intractable epileptics.

Reynolds and Shorvon[5] recently compared the results of therapy using one medication (monotherapy) to the results of therapy using more than one medication (polytherapy). They found no significant difference in the efficacy of carbamazepine (CBZ) or phenytoin (PHT) for the treatment of previously untreated adult epileptics. The seizures of approximately 70%–75% of patients could be controlled completely with one drug. They found no evidence that the addition of a second anticonvulsant was beneficial. Our experience with monotherapy has been similar.[6] Of 20 patients with intractable seizures who were taking two or more anticonvulsants, 8 became seizure free with monotherapy and 7 had their seizure frequency reduced by two thirds. No patient suffered any exacerbation of their epileptic condition. Most of the patients reported a decrease in side effects from the medication. Schmidt[7] evaluated 36 patients with intractable complex partial seizures; all were taking two anticonvulsants. The regimen of these patients was gradually converted to monotherapy. The change was accomplished without an increase in generalized seizures or status epilepticus. Eighty-three per cent of these patients had no increase in complex partial seizures, while 36% noted a decrease in seizure frequency. Two patients became seizure free. Only 17% had an increased number of complex partial seizures. Schmidt[8] also studied 30 adults with intractable complex partial seizures who continued to have epileptic attacks despite adequate treatment with CBZ, PHT, phenobarbital (PB), or primidone (PRM). In this study, a second anticonvulsant was added to the first, and the dosages were adjusted until clinical toxicity was evident. A reduction of seizure frequency by more than 75% occurred in only 4 patients; the remaining 26 either did not benefit from taking the second drug or experienced an increase in seizure frequency. The message of these studies seems clear: patients with intractable seizures usually can be treated with a single, nonsedating anticonvulsant.

Serum anticonvulsant levels

The usefulness of the blood serum levels of antiepileptic drugs has been discussed by Kutt and Penry,[9] but they were careful to point out that "one should not treat the levels per se but use them as information in formulating the clinical judgment for each patient." A recent study by Beardsley et al[10] showed that although information about anticonvulsant serum levels was readily available, seizure control in a large population group was not improved because this information was not used appropriately during therapeutic decision-making processes. Serum anticonvulsant levels should serve only as a guide for treatment and can be useful for detecting noncompliance and variations in metabolism among different patients. The "therapeutic range" should be the serum level at which the seizures of many patients will be controlled. Nevertheless, patients may still experience adverse side effects from the medication when their blood level is in this range, and the seizures of some patients can still be controlled with a blood level that is either higher or lower than this range. For example, the therapeutic level of PHT is frequently given between 10 and 20 μg/mL. The seizures of some patients, however, may be controlled with a serum level of 7 or 8 μg/mL.

The seizures of other patients may not be controlled unless the serum level is significantly higher (30 or 35 μg/mL). When taking a single drug, many patients can tolerate higher serum levels and experience no significant side effects. Accordingly, if a person is continuing to experience seizures with a PHT level of 20 μg/mL, the dosage should be increased cautiously. PHT blood levels may increase disproportionately to an increase in the dosage of the medication because, at higher blood levels, metabolism follows zero-order kinetics.[11] Therefore, when increasing the dosage of medication in a patient who has a PHT serum level ≥10 μg/mL, the adjustment should be small. The patient should be examined after one to three weeks to check for evidence of toxicity and to measure the serum anticonvulsant level again. Other commonly used anticonvulsants do not follow zero-order kinetics, and a large jump in serum anticonvulsant levels is uncommon with a small adjustment in dosage.

Protein binding

In addition, the degree of protein binding of anticonvulsants varies in each individual. Consequently, because of the interference of other medications with protein binding and because the unbounded serum fraction is the biologically active agent, measurement of free or unbound anticonvulsant levels can lead to an assessment of drug toxicity and response to therapy. When possible, we commonly measure unbound anticonvulsant levels of difficult patients undergoing high-dose monotherapy.

Treatment strategies

As stated by Gram et al,[12] no studies have shown any one of the primary anticonvulsants (PHT, CBZ, PRM) to be superior to another in the treatment of complex partial seizures. Therefore, it would seem logical to preferentially use the drugs that would result in fewer side effects for the patient. We prefer to begin treatment with either PHT or CBZ, but if the patient is already taking a reasonable amount of PB or PRM and is experiencing no side effects, the dosage can be increased before anticonvulsant medication is changed. If the patient is taking several anticonvulsants, but is being seen on an outpatient basis, we generally taper and discontinue each additional medication one at a time during a two- to four-week period. If the patient is hospitalized, however, we discontinue several anticonvulsants simultaneously and taper the dosages more rapidly. Sedating medications (PB, PRM, or the benzodiazepines) should be discontinued first. When the patient is taking only one anticonvulsant, the highest serum level possible should be obtained without producing significant side effects. If PHT is being used, two daily dosages of Dilantin will minimize fluctuations in the serum anticonvulsant level. If CBZ is being used, dosages should be given at three separate intervals. While in the hospital, administration of CBZ four times daily is achievable; however, in ambulatory outpatients, the increased number of times to self-administer the medication increases the likelihood of noncompliance. Consequently, the number of dosages is reduced to three. If the patient's seizures are not controlled with the first anticonvulsant chosen, other nonsedating primary anticonvulsants should be used. Dosages of the first drug should be rapidly tapered, then discontinued; at the same time, treatment and subsequent dosage adjustment with the second drug should be started. If the second major anticonvulsant fails to control the seizures at slightly subtoxic doses, PRM should be tried. PRM is metabolized to phenylethylmalonamide (PEMA) and PB.[13] Although PRM, PEMA, and PB are all anticonvulsants, the mechanisms of action of PRM and PB appear to be different.[14] PHT and other drugs enhance the conversion of PRM to PB.[15] Bourgeois et al[16] have demonstrated that nicotinamide can slow the conversion of PRM to PB and were able to obtain higher serum levels of PRM in a few patients by administering nicotinamide along with PRM. This strategy resulted in improved seizure control for some patients, but side effects involving the gastrointestinal tract occurred. High PRM levels can also be obtained if the drug is administered by itself at high dosages.[17] If neither PHT, CBZ, nor PRM fully control a patient's seizures, the two drugs which have previously been shown to be most effective in that patient are used. Yet, the number of patients who will experience a significantly improved condition due to a combination of anticonvulsants will be small. Also, increased side effects can be expected. We increase the dosage of the medications until the patient experiences side effects, then we reduce the dosage slightly. If the combined use of the two primary anticonvulsants does not result in improvement, the most effective primary anticonvulsant may be employed in conjunction with one of the secondary

anticonvulsants (valproic acid [VPA], methsuximide, benzodiazepines, acetazolamide, and progesterone agents).

Methsuximide

Methsuximide is one of the members of the succinimide family and was introduced for clinical usage in 1957 as a medication for absence seizures. This drug rapidly metabolizes to the compound N-desmethylmethsuximide, which is active and has a long biological half life.[18] Wilder and Buchanan[19] reported that the addition of methsuximide to the pre-existing drug regimen of 21 patients with refractory complex partial seizures resulted in improved seizure control. The average number of seizures decreased from 5.8 to 0.9 per week. Fifteen patients experienced 90%–100% control of their seizures. Unfortunately, the validity of this study is questionable since the patients were on multiple medications and the various drug levels were not reported. Methsuximide interacts with other anticonvulsants and frequently results in significant elevations of PHT and PB.[20,21] Whether the improvement noted by Wilder and Buchanan was secondary to the methsuximide or increased levels of other anticonvulsants or due to a combination of other factors cannot be determined from their data. Browne et al[21] recently reported the effects of methsuximide on 26 patients with intractable complex partial seizures. These individuals were all taking PHT, PB, PRM, or CBZ or a combination of anticonvulsants. Eight patients were dropped from the study because of evidence of drug toxicity; 3 others were dropped due to an increased number of seizures. Four patients experienced complete seizure reduction, 4 experienced 50%–99% seizure reduction, and 7 experienced 0%–49% seizure reduction. In all, only 31% experienced a greater than 50% reduction in their seizures. The drug interactions were also important: significant elevations of PHT, PB, and PRM levels were evident in most of the patients taking these drugs, but a significant reduction in the serum CBZ level was evident in most patients taking CBZ. The authors found that the biological half life of N-desmethylmethsuximide was increased to 72 hours because of the inhibition of its metabolism by the other anticonvulsants. Tassinari and Roger[22] stated that methsuximide is ineffective for the treatment of complex partial seizures. We can recall only a few of our patients who benefited significantly from this medication; many complained of side effects. To our knowledge, no systematic study of methsuximide used as a single agent for treatment of complex partial seizures with monitoring of drug levels has been carried out.

Valproic acid

Although VPA may be of use in the treatment of complex partial seizures, it is less effective than when used to treat generalized seizure disorders.[23] Approximately a quarter to a third of patients with complex partial seizures have a 75% or greater reduction in their epileptic attacks with VPA treatment.[23,24] VPA may be more effective for the treatment of children with complex partial seizures. Thirty-eight children with partial epilepsy (not broken down into complex partial vs. simple partial) were studied and 56% had a greater than 75% decrease in seizure frequency.[26] Details of concurrent anticonvulsant therapy were not provided, however. In the study by Coulter et al,[27] 44% of the children evaluated experienced a greater than 75% decrease in the frequency of their seizures, while 78% experienced a more than 50% decrease in the frequency of their complex partial seizures. Adams et al[28] found a greater than 50% decrease in seizure frequency in 3 of 5 adults treated with VPA for intractable complex partial seizures. Bruni and Albright[29] found that 12 of 24 patients with intractable seizures had a greater than 50% reduction in seizure frequency when VPA was added to pre-existing anticonvulsant treatment. Only 5 of the 12 patients maintained an improvement; however, patients with more than eight seizures per month did not seem to respond as well to therapy after three months. The administration of VPA to a person receiving PHT will frequently result in a decrease in the total serum PHT level but an increase in unbound PHT because of competition from VPA and PHT for protein-binding sites. After several weeks, the total PHT level will gradually increase because of inhibition of PHT metabolism.[30] An increased serum PB level will frequently develop in patients taking PB after VPA is added to their treatment.[30] The dosage of PB should be reduced by one quarter to one third when VPA treatment is initiated. Patients taking CBZ who receive VPA do not usually experience clinical difficulties. VPA can displace CBZ from its protein-binding sites, however, and could result in toxicity without an increase in serum levels.[30] The effects of

adding VPA to the treatment of a patient taking PRM are also unclear, but the level of PB derived from the metabolism of PRM may rise significantly.[30] VPA should be used only as a secondary drug to treat intractable complex partial seizures. Careful monitoring of total and possibly unbound plasma levels of all anticonvulsants should be done.

Benzodiazepines

Benzodiazepines are of questionable benefit for the treatment of complex partial seizures[31] and must be considered secondary anticonvulsants. Troupin et al[32] found clorazepate to be as effective as PB in the treatment of intractable complex partial seizures in patients whose treatment primarily involved an anticonvulsant such as PHT. Troupin et al discovered no significant side effects with clorazepate treatment; all patients receiving PB complained of drowsiness. Berchou et al[33] reported a significant decrease in seizure frequency in only 15% of patients given clorazepate for intractable complex partial seizures; an additional 30% experienced a partial decrease. The dosages were determined by evidence of seizure control or toxicity; otherwise, 3 mg/kg was used. We have not found clorazepate to be particularly helpful for those with intractable complex partial seizures. Patients frequently complain of drowsiness and other side effects with benzodiazepine treatment. If clorazepate is to be used at all, it should be used with PHT or CBZ since the side effects when given with sedating anticonvulsants may be marked.

Acetazolamide

The pharmacology and usage of acetazolamide for epilepsy have recently been reviewed by Woodbury and Kemp.[34] The drug is a carbonic anhydrase inhibitor and presumably its action is via this inhibiting mechanism. As a secondary drug, acetazolamide is effective for many epileptic disorders. It has also been used for intermittent treatment of catamenial epilepsy (increased frequency of seizures before and after menstruation). The daily dosage of acetazolamide is approximately 10 mg/kg. Higher dosages may increase the severity of side effects without increasing therapeutic benefit since the carbonic anhydrase of the brain is maximally inhibited at this dosage. Somnolence and paresthesias are the usual complications. Forsythe et al[35] used acetazolamide in 14 pediatric cases of complex partial seizures uncontrolled with CBZ alone. Nine patients (64%) had a greater than 75% reduction in seizure frequency; this effect was prolonged. While several children had increases in CBZ levels after the addition of acetazolamide, the authors were unable to attribute the anticonvulsant activity of acetazolamide to this secondary effect. We have used acetazolamide in a few patients with intractable complex partial seizures and have not been impressed with its effectiveness.

Norethisterone

As discussed in the review by Newmark and Penry,[36] anecdotal reports suggest that progestational agents can be used to treat catamenial epilepsy. In a prospective study, Dana-Haeri and Richens[37] did not show a decrease in seizure frequency when low-dose (1 μg/day) or high-dose (15 μg/day) treatment with norethisterone was compared to a placebo. If a patient's complex partial seizures increases before or during menstruation, a progestational agent may be used therapeutically, but the effectiveness of such treatment is still unproved.

Conclusion

Intractable complex partial seizures are best managed by establishing an exact seizure diagnosis before initiating treatment. This process frequently requires hospitalization of the patient. Initially, treatment should consist of one primary, preferably non-sedating, anticonvulsant. The dosage of the medication should be increased gradually until seizures are controlled or drug-induced side effects develop. The serum anticonvulsant level is a guide for therapy. If the first anticonvulsant chosen does not control seizures, the other primary anticonvulsants should be tried one at a time. Only if PHT, CBZ, and PRM fail to control the seizures individually should polytherapy be tried. A logical sequence of this combination treatment consists of using the two best primary anticonvulsants; if they are unsuccessful, then the best principal anticonvulsant and one of the several secondary anticonvulsants should be used. While such secondary medications are less likely to help, their use is justified by the intractability and frequency of seizures experienced by many patients.

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