Workshop
Antiepileptic drug therapy: monotherapy vs polypharmacy

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Dr. Bourgeois: Often in the treatment of epilepsy, when we are not successful with one drug, we attempt to combine two antiepileptic agents. Our purpose in doing so is to achieve a reduction in the number of seizures, but how do we think the two drugs will work together? Theoretically, there might be two reasons for combining two antiepileptic drugs. Perhaps we hope to achieve a wider antiepileptic spectrum with two or three agents than with one. If a patient, for instance, has more than one type of seizure and each type may respond to a different agent, then we may believe it better to administer two agents; or we may believe that different mechanisms may be involved in one specific seizure type and that two drugs are more likely to affect the different mechanisms; or we may believe that two drugs administered together will have an additive or enhancing effect.

Two drugs can demonstrate a combined action, or pharmacodynamic interaction, in three possible ways. If the combined action of two drugs is equal to the sum of their single actions, the interaction is additive. If the combined action is larger in quantity or degree (more than the expected sum of the two drugs added), the interaction is supra-additive (potentiation). If the combined action is less in quantity or degree than the sum of the individual drugs, it is infra-additive (antagonism).

Merely checking the anticonvulsant effect in order to measure the pharmacodynamic interactions of two antiepileptic drugs is not too helpful because toxicity may also be additive or supra-additive in the same combination of drugs. If one attempts to evaluate interactions in a quantitative fashion which is significant and helpful, one must look at the therapeutic index, that is, the ratio between the toxic dose (or concentration) and the effective dose (or concentration). Suppose, for example, that one raises the dosage of two drugs to the maximum tolerated level; the anticonvulsant effect is potentiated, but the toxicity is not. Then the therapeutic index of the combination will be better than the therapeutic indices of the two components. Because of methodologic limitations and requirements, studies in this area are very difficult to carry out in patients with epilepsy. We and a number of other investigators, therefore, have used an experimental mouse model of epilepsy in order to study the therapeutic indices of various antiepileptic drugs alone or in combination.

In the experimental model devised, seizures were provoked either by electroshock or by pentylenetetrazol; neurotoxicity, signified by incoordination and sedation, was determined by the rotorod test. All results were based on brain concentrations of the drugs in order to avoid any interference from pharmacokinetic interactions. On the basis of brain concentration, the concentration at which 50% of the animals were protected against the artificially induced seizures was determined (EC_{50}). Similarly, the concentration at which 50% of the animals showed neurotoxicity, ataxia, or sufficient sedation to fall off the rotating rod was determined (TC_{50}). The therapeutic index was then TC_{50}/EC_{50}. We also looked at the fractional effective concentration (FEC), or the effective concentration of a drug administered in combination with another drug, compared to the effective concentration of the drug administered alone.

Using this methodology and this mouse model, we evaluated a number of antiepileptic drug combinations. Phenytoin and phenobarbital are two drugs that have been combined for many years; in fact, it used to be not uncommon to start patients on a combination of the two drugs. It is well known that phenytoin alone has a much better therapeutic index than phenobarbital alone because it is much less sedative than phenobarbital. When the two drugs are administered together at a constant brain concentration, the combination has a purely additive interaction (1 + 1). The neurotoxicity of the combination proved to be infra-additive. The therapeutic index of the combination was still lower than the therapeutic index of phenytoin alone. When phenobarbital and phenytoin are administered together at the same dosage, one gets a higher dose of phenytoin than if phenytoin is administered alone. There is an acute pharmacokinetic interaction, which makes one believe that the combination is providing a supra-additive interaction. But the interaction is purely pharmacokinetic and is pharmacologically not supra-additive.

When one gives two anticonvulsant drugs together, what the drugs have in common is their anticonvulsant activity. What the drugs do not necessarily have in common is the same toxic activity; toxicity can be of different types and therefore not necessarily additive. The FEC index for the combination of phenytoin and phenobarbital confirmed our determination of the therapeutic index of the combination.

Using the same model, other investigators have tested the combination of phenytoin and carbamazepine; they found that the anticonvulsant effect of the combination was purely additive; the toxicity was also additive. The therapeutic index of the combination was not superior to the therapeutic index of either of the two drugs. Testing of carbamazepine and phenobarbital demonstrated another additive interaction against the seizure model and a purely additive toxic interaction.

Both valproate and ethosuximide are effective against absence seizures and certain myoclonic seizures. When tested against the pentylenetetrazol seizure model, their combined activity is purely additive; their combined toxicity is infra-additive. The FEC index of the combination suggests, in fact, a strikingly infra-additive toxicity.

Most drug combinations tested according to this model demonstrate antiepileptic interactions which are additive. The only supra-additive interactions noted were between phenobarbital and primidone, and between phenobarbital and the other metabolite of primidone, phenylethylmalonamide.

All of these findings are what one might actually expect on the basis of the assumption that anticonvulsant drugs have a common anticonvulsant action but not necessarily a common neurotoxicity.

Dr. Schmidt: When the clinician adds two drugs together, he or she may run into pharmacokinetic interactions. As an example, you may have difficulties in reaching an effective therapeutic concentration with the comedication, let's say, of phenobarbital and carbamazepine. If I am correct, your model excludes these clinically relevant pharmacokinetic interactions.

Dr. Bourgeois: Absolutely. That is why we have to use brain concentrations, because we really want to get the pharmacodynamic interactions, and we want to correct just for levels. We monitor patients, we also look at levels; so, we do take into account pharmacokinetic interactions. What we are interested in is what happens when you control that and look at levels: what happens with the interactions? We do want to rule out pharmacokinetic interactions.

Actually for many years, and on the basis of several reports, it has always been said that the interaction between phenobarbital and phenytoin is supra-additive. All these studies were based on doses. Leppik, in his study in 1977, examined that problem using concentrations and doses. In this study we also looked at concentrations and doses. When you give phenobarbital and phenytoin together at the same dose, you get a higher phenytoin concentration than if you give phenytoin alone. Therefore, there is an acute pharmacokinetic interaction which will actually make you believe that there is a supra-additive interaction. But the interaction is pharmacologically not supra-additive; it is a purely pharmacokinetic interaction.

Dr. Schmidt: From a clinical point of view, you present as one side of the coin the pharmacodynamic side; but the clinician also monitors the pharmacokinetic interaction. This sum then forms the clinical impact of the combination.

Question: Can you comment on different kinds of benzodiazepines?

Dr. Bourgeois: I have not studied benzodiazepines. It has been done, usually on the basis of dosages. There is evidence that benzodiazepines, for instance, will actually potentiate the effect of barbiturates. This is not surprising, because they both work, probably, at the chloride ionophore. It has also been shown in vitro that the action at the level of the benzodiazepine receptor

and the chloride ionophore is potentiated by benzodiazepines. Yes, I would say that benzodiazepines do potentiate the action of barbiturates.

Dr. Schmidt: If that were so, adding two drugs with different mechanisms of action should produce a better result in your model than they do. When you combine, let's say, phenytoin, which has no GABAergic mechanism, with phenobarbital, which has a GABAergic mechanism, you might expect better results than you showed us. How do you explain that?

Dr. Bourgeois: We are using one seizure model here, which is electroshock. It is likely that, no matter what the mechanism of action, only one final path is activated or affected by the two drugs, so that the final mechanism of action of the two drugs is neurophysiologically the same; therefore, their effect is additive.

Dr. Schmidt: Another issue relates to the seizure model. If you take the maximal electroshock model, you may end up determining an effective dose for maximal electroshock only, but not for other seizure models. If you take a model for focal seizures, you may need higher effective doses. If your model can be applied to the clinical situation, it really applies mainly to generalized tonic-clonic seizures. Is that correct?

Dr. Bourgeois Yes. I think it is very hard to extrapolate to any particular seizure type, except for the fact that we know that drugs that are effective against electroshock usually are effective against both generalized and secondary generalized, and partial seizures.

Question: Just as there are multiple factors in the therapeutic index, there should be multiple factors in toxicity. We also obviously take that into account in the clinical situation. Drugs interact elsewhere than in the brain.

Dr. Bourgeois: That is right. But again, the question is, how do drugs interact together? One has to start with one parameter; then one can start to look at ten or 15 parameters. It is a matter of time and years.

Dr. Rothner: We want to consider the question of monotherapy vs polytherapy from the viewpoint of what is most effective for the general clinical pediatric neurologist who is treating patients with certain types of epilepsy. If one looks first at the prevalence of seizure types in the epileptic population, approximately 60% to 70% of the patients will be relatively easy to treat. For these patients, treatment with a single antiepileptic agent will yield the best clinical results with the least clinical toxicity. Patients with seizures resistant to single-drug therapy are likely candidates for polytherapy. They were once roughly characterized by Ducha-ney in a lecture in which he classified seizures as "good, bad, and ugly." The "good" seizures might be absence seizures or generalized tonic-clonic seizures in a well person, or even juvenile myoclonic seizures. The "bad" and "ugly" might consist of Lennox-Gastaut syndrome, West syndrome, and complex partial seizures. Patients with the latter type of seizure will be the most difficult to treat. They are found most frequently in the pediatric age group when the development of the child is at a critical stage and is being adversely influenced by frequent seizures on a daily or even hourly basis. Seizures in patients of these types are brief and repetitive; they are commonly seen in association with and perhaps even increasing the burden of mental retardation. The EEGs are highly abnormal. Such patients are difficult to treat; and the prognosis, with regard to life outcome and to stopping the seizures, is poor. At diagnosis, retardation is significant; but at follow-up it is even more severe. Normal patients with infantile spasms are very rare.

Polytherapy for such patients is not something new. Some years ago we found we had an extremely successful treatment for epilepsy, but the Food and Drug Administration removed it from the market because it had multiple components. The question remains: what do we do for patients with uncontrolled seizures?

Characteristically, one selects a single drug which one believes is, first, efficacious; second, least toxic; third, least expensive; and fourth, carries a statistical likelihood that the patient will respond. One starts the patient on a very small dosage of the drug and gradually builds the drug up into a therapeutic range. In other words, one maximizes therapy with a single drug. If the patient responds, that is fine. If the patient does not, does one again strive for monotherapy with drug two...and then drug three? Only a minority of patients who did not respond to drug one will respond to drug two if it is in the same category of agents as drug one. Basically, if a patient is drug-resistant, one is able to identify that quite clearly.

We all know that the use of multiple drugs together entails the risk of significant side effects. Despite the possibility of an additive effect, multiple-drug therapy also entails the chance of drug-drug interactions which may influence the clinical response of the patient. That is the significant dilemma facing us in clinical medicine. The answer to the question of when to start polytherapy is very simple: only when it is necessary. If multiple single drugs, administered in maximal dosages, have failed to secure a response, one has to weigh the potential benefit of using two medications together.

We do not as yet have any properly controlled proof that multiple drugs used together are really more effective, but there are clinical impressions to that effect. I personally start polytherapy when the patient's seizures have been uncontrolled on multiple monotherapies.

In polytherapy, which drug should one start with? Obviously, the first drug is the easiest to choose, because each drug has a known record of anticonvulsant effect for specific types of seizure. If we are dealing with a child who has myoclonic seizures or grand mal seizures, we know that our chances of success are reduced. As to the choice of a first drug and then a second (or third) for polytherapy, we do not have a body of carefully controlled data on which to base our opinion. Instead, we have the favorite choices of thousands of clinicians. I myself, for instance, have no idea of what a "better combination" is! I know that I have frequently used a combination of carbamazepine and valproic acid; but we have recently seen a sufficient number of patients with normal or therapeutic carbamazepine levels, or with high free levels, who have had such high toxicity that we had to reduce the combination.

Possibly used on an intermittent basis, the benzodiazepines are effective combination drugs with valproic acid. As a group, the benzodiazepines can be effective under various circumstances. We must now seek, I believe, to identify a specific group of patients with as consistent a type of seizure pattern as can be determined, and then begin to look at the results of long-term therapy. In terms of less toxicity and better control, our patients seem to have done better on nitrazepam. Nitrazepam also has a longer duration of efficacy than clonazepam. We have also used rectal diazepam with some success. That agent is not available in the United States in suppository form, but the IV solution of diazepam can be adapted to this purpose by an ingenious hospital pharmacist. We have had some successful experience with lorazepam, other than in treating status epilepticus, as an "add-on," temporary, stopgap measure to prevent clusters of seizures. For some patients, it is effective in improving the quality of life, once one is willing to accept the premise that, for all practical purposes, the patient's seizures cannot be controlled.

The only way we are going to be able to answer questions about polytherapy usefully is to begin to study them systematically: first, by knowing exactly what we are attempting to treat, and then by starting prospective trials of given combinations. But the best combinations, I think, are yet to be identified by thorough studies.

Question: Dr. Rothner, would you comment on the use of gamma globulin? I have one patient with whom our hematologist actually fractionated the gamma globulin, found the two fractions to be low, and has suggested gamma globulin infusions.

Dr. Rothner: What we have seen is that anti-inflammatory agents, whatever their potential effect, can have a beneficial effect on seizures. We look at the use of ACTH in infantile spasms, and we get our first inkling that something is about to happen. Now we look at the therapeutic use of agents such as gamma globulin in patients who have idiopathic thrombocytopenic purpura and other immunologically related disease.

On the one hand, we use gamma globulin as a therapy for an immunologic disease. On the other hand, in the case of ACTH, we use an immunologic therapy for seizures. In between, we have a group of patients who are quite interesting. We have a group of patients with intractable childhood epilepsy, who have an IgG subclass 2 deficiency. That is the one most commonly identified. These patients may or may not have an increased rate of infection. Those of us taking care of many patients with epilepsy realize that if you have "X" as a control, many times that control is lost when the patient gets sick with a fever, or some other illness—even if he or she does not require multiple antibiotics.

The question would be, then, if we replace the IgG2 in these patients, first, would the patient's seizure control improve; second, would there be fewer infections, and therefore less difficulty with seizure control? There is a third aspect to IgG as a therapeutic agent. In a patient who has neither IgG subclass deficiency nor recurrent infections, if we give immunoglobulin as a medicine, does immunoglobulin make the seizures better?

We are going to exclude from this discussion the patients who have IgA deficiency. First, IgA cannot be replaced by the gamma globulin preparations that are available: and, second, we are not sure how it relates to seizures. We do think that, for example, phenytoin can decrease IgA levels. If we are talking, therefore, about patients with intractable childhood epilepsy, with or without recurrent infections and with or without subclass deficiency, the question is, does the medication help?

I recently had the opportunity to review the litera-

ture on this question. What we have is a large number of abstracts and one or two articles. Abstracts, to me, are almost like testimonials. The truth of the matter is that there have not been enough well-documented studies.

What we are trying to do is look at three groups of patients, using the patients as their own controls, giving them gamma globulin infusions every three weeks, and then looking at those groups of patients that I identified to see if there is an improvement.

Question: In the use of some of these combination drugs, there is a great tendency on the part of individuals not to monitor the drug concentrations. This is particularly true of ethosuximide. If there was ever a drug that did not have a fair shake, it is ethosuximide. We call ethosuximide a failure without ever having tried to achieve higher levels. Pediatric neurologists have a great tendency not to monitor that drug. I think, clinically, we could learn a lot more about it, and would find it much more effective if we would monitor it.

Question: Lorazepam is supposed to be much longer-acting. I know it is used for status now. What is your experience with that?

Dr. Rothner: Again, I think the benzodiazepines, as a group, can be effective under different circumstances. I think one is now obligated to identify a specific group of patients with as consistent a type of seizure pattern as one can, and begin to look at long-term therapy. We have felt that nitrazepam is better for our patients, in terms of less toxicity and better control, and it has a longer duration of efficacy than clonazepam has.

My experience with lorazepam, other than in status epilepticus, is as an add-on, temporary, stopgap measure to prevent clusters of seizures. For some patients, it is effective in improving the quality of life, once you are willing to accept the premise that this patient's seizures, for all practical purposes, cannot be controlled. That is difficult for somebody treating epilepsy.

Dr. Schmidt: I want to invite you to look with me for a few minutes at a typical clinical situation. Anyone who treats many patients with epilepsy is faced with the fact that some patients, whether they have Lennox-Gastaut syndrome, another form of multifocal epilepsy, or complex partial seizures, have not responded to some of the best drugs available. Documented nonresponse failure means that the patient received the drug in a dosage that caused side effects, but the seizures still persisted.

Then one goes through the same process to add a second drug. We know that once patients with complex partial seizures are resistant to a single drug, only 10% to 15% will benefit from adding a second drug. The estimates for addition of a third drug have never been studied adequately, but I think they would be even lower.

When you are faced with a patient with whom you have failed, what do you do? It is very easy to understand that there is an urge to do something—to calm the mother, to calm yourself. You are supposed to help the patient; so what do you do? You add another drug. You have done something; and the parents may be happy for a while, because you have done something in an urgent situation.

But the truth of the matter is, if you look at it with a cold eye, what you have done has not changed the seizure frequency much, and you have added side effects for that patient. Then comes the crucial question: Wouldn't that patient be better off with just as many seizures and fewer drugs? This is easier said than done.

If you have an epileptic patient on two or more drugs and you ask whether it is useful to reduce antiepileptic-drug polypharmacy when seizures cannot be controlled, you are faced with a number of questions. First, if there are several drugs, which one do you reduce first? Secondly, how fast do you reduce the dosage of that drug? How can you predict the risk-benefit ratio? When do you reintroduce the previous medication if seizures continue or increase? Is it of any value to wait for a while, to calm down, to think you may be better off once you are through that stormy period?

The answers to those questions are very limited. What I offer you as an answer is not hard evidence, but one way of handling such a situation, without saying that controlled studies are not necessary. Monotherapy is a virtue. I have written some papers supporting monotherapy. If you ask me how many patients in my private practice receive more than one drug, I know the answer exactly: 37%. What are the issues faced when you treat a patient with several drugs?

The reason polypharmacy is used is that probably, in a small minority of epileptic patients, it produces better seizure control than a single drug. That is, 10% to 20% of the patients do better with two drugs than with one. Even that percentage has never been adequately demonstrated with placebo controls. So what I offer you is the best of uncontrolled studies, and that is dismal: 10% to 20%.

In my mind, a major reason that patients receive more than one drug is the pressure on clinicians to "do something" for patients with uncontrolled seizures.

Certainly, we lack knowledge about differences in the efficacy of individual drugs; and we really do not know which combinations are better than others. We treat by a trial-and-error system. There is nothing wrong with trial and error, if you reduce the drug again after you have found that the addition did not help the patient.

A number of reasons speak against polypharmacy. There is suggestive evidence that chronic toxicity is higher with multiple-drug therapy than with single-drug therapy. Efficacy may be poor because of interactions, if one drug causes an increase in the metabolism of the other drug, or if one drug causes a decreased resorption. As a clinician, you have the difficult job of evaluating what you are doing, and what the individual drug is doing in the combination.

Finally, I want to offer you a very disturbing notion: that combination of drugs which you select may actually lead to an exacerbation of seizures. Suggestive experimental evidence and clinical evidence both support the idea that antiepileptic drugs may, in fact, exacerbate epilepsy. Ten years ago, at the National Institutes of Health, I participated in a study in which patients with complex partial seizures, uncontrolled by two drugs, were reduced to single-drug therapy. With a patient who received phenytoin and primidone, we stopped the primidone, and monitored paroxysmal discharges, total seconds, with telemetry. When primidone was discontinued, the EEG got much better, and the patient became completely controlled. Now, you may say this is an individual case. It is, but it offers us an insight.

In the case of another patient in that series, a patient with generalized tonic-clonic and complex partial seizures under treatment with several drugs, we again discontinued primidone. We saw a transient increase in seizures, but then the patient was really better off than before, and had less toxicity. These two cases forced me to think about whether our concept of adding a second drug when the first one has failed not only is not good for side effects, but is also really not useful for seizure control.

Another investigator performed a very nice experiment in previously untreated patients with complex partial seizures. He randomized treatment with carbamazepine alone (50 patients) and with phenytoin alone (50 patients). The treatment failures of each group received the combination, and 15% of them profited from the administration of the two drugs. The investigator did not go further and determine whether those patients whose seizures were controlled by the combination would have had them controlled just by replacing either drug. I can understand, however, why he did not do that, because once the seizures are well controlled, you do not disturb the patient without any direct pressure. I would imagine, in fact, that it is very useful not to find out in such patients whether they really would have been better off with one drug. It is best sometimes to leave well enough alone.

We know that multiple-drug therapy is associated with an increased risk of side effects. In a typical study of the pediatric population, you see a 22% incidence of side effects with single-drug therapy; of 34% with two drugs, and with three or more, 44%. What most clinicians do (but rarely report) is to reduce the dosage of the first drug when they add a second drug, hoping to make the combination effective and reduce the chance of toxicity.

Patients come from faraway places and expect me to produce miracle cures. I am faced with the problem that such patients, often with Lennox-Gastaut syndrome, are under treatment with two or more drugs. In one group of such patients, I tried to reduce the number of antiepileptic drugs they received. In no case in that group did I succeed in cutting therapy to a single drug. Patients were reduced from three to two drugs, from four to three. What I specifically sought to do was to reduce the number of barbiturates, either phenobarbital or primidone; and in four out of five such patients, I did succeed in reducing phenobarbital and primidone to zero.

What I thought I would be doing was to help these patients with side effects. Wrong. I was disappointed, because most of the patients continued to have side effects. Why? Because I increased the dosage of the remaining drug, since I was afraid they might have more seizures.

Obviously, reduction of polypharmacy does not immediately lead to a reduction in side effects. What happened in these patients was that the number of generalized tonic-clonic seizures dropped (these are six-month controls) by a mean of 50%. Quite unexpectedly, I did not succeed in reducing the side effects; instead, I replaced them, by replacing the side effects of barbiturates with those of other drugs. But seizure control improved.

The reason for this phenomenon is not perfectly clear, but one major influence may be the fact that sedative medication may indeed increase generalized seizures, that is, myoclonic or absence seizures.

In another study, two-drug therapy was reduced to single-drug therapy in patients with complex partial seizures. Changing from two drugs to a single drug

reduced the number of seizures in 10% of the patients by more than 75%. The median seizure frequency, however, was not different in the two groups.

Again, I had hoped to succeed in reducing the side effects in those patients, but again, it did not really work. The patients had the same incidence of side effects. That may be related to the fact that I had tried to increase the dosage of the remaining drug as high as possible.

What follows from these few cases? It follows that reduction of polypharmacy is something that is useful for a minority of patients because they may have fewer seizures. It is not certain that it will reduce clinical neurotoxicity. In addition, it takes time to check cognitive side effects upon the reduction of polypharmacy. Neuropsychologists believe it takes 6 to 8 months after the reduction of barbiturates in a combination for cognitive function to improve in a patient.

If you are faced with a situation in which primary drugs in single and combination therapy have failed and second-line drugs have been tried, there is one option: slow reduction of the number of drugs. If you ask me what "slow" is, I can tell you that nobody knows. I can tell what I call "slow," which does not lead to status epilepticus, if you increase the dosage of the remaining drug as far as possible: you reduce phenytoin by 50 mg per month, phenobarbital by 100 mg, primidone by 250 mg, and valproate by 500 mg per month. But these are not scientific data; there are no useful data available on whether these drugs differ in terms of their withdrawal seizures.

We are entering an era where the rationalization of polypharmacy offers us an option to reduce the number of seizures in a minority of patients without causing an undue increase in the number of seizures. I want to caution you, however: if you are sitting all by yourself in an office and do not have a department behind you and you are trying to reduce polypharmacy, be careful. Explain to the parents what they are heading for: namely, a very rough period of a transient increase in seizures. All my patients receive rectal diazepam as an emergency treatment. They take it home. They are told, if they have more than one seizure, to use rectal diazepam to stop the series of seizures, and to call me when there is another seizure, but not to change the medication.

Reduction of polypharmacy is one of the most severe tests of the relationship between a doctor and a patient. If you succeed in holding off any decision for reintroduction for 6 to 8 weeks, you are over the worst.

Finally, it is useful to have a dual approach to intractable epilepsy. First, see whether single-drug treatment with the maximum clinically tolerable dosage works if it is really necessary to use the highest dosage. If you find that does not work, reduce the dosage and reduce the number of drugs, to see if you can reach a compromise where the number of drugs is lowest, without an undue increase in seizures.

We have some time now for discussion.

Participant: May I comment briefly on rectal administration of anticonvulsants? We have had the experience of using a number of them, including diazepam and lorazepam. Although one finds that lorazepam has a little longer action, almost invariably, families do not seem to like lorazepam as much as diazepam because they feel it leaves the child less responsive. Could you comment on that?

Dr. Schmidt: In the United States, lorazepam is widely given, while in Europe diazepam is the drug of choice. In this country, one has about a 30% failure rate with rectal diazepam, for several reasons. First, parents prefer to bring the child to the hospital anyway, instead of giving rectal diazepam at home. Second, they arrive too late, and the seizure has stopped by itself. Third, in some groups there are problems in administering solutions of drugs. Fourth, parents perhaps do not fully understand the method of administration: one must press down on the tube to force out the solution, press down and not let the solution be sucked back; and if diarrhea occurs, one has to attempt administration again. But if there is good counseling, most parents are very happy with rectal diazepam.

Participant: I would like to make a plea for the usefulness of looking at the behavioral aspects of multiple-drug therapy. We know that any time a child or adult gets drowsy on medication, he or she is then more likely to have more seizures. This can be documented by looking at the EEG; the patient begins to put out more seizure activity. Perhaps we could combat this tendency by making sure that the patient stays alert.

Dr. Schmidt: Sedation, in fact, is the major factor in the increased incidence of seizures in patients with generalized seizures. The EEG is a helpful monitor in the sense that it slows down upon addition of another drug. It is not very helpful in predicting the long-term course of a patient. If you monitor the EEG, it is not very reliable in telling you which patients will have a drastic increase in number of seizures. The failure rate associated with the reduction of polypharmacy ranges anywhere from 15% to 50%, depending on how long you have the nerve to wait before you introduce the

medication. The EEG is not very helpful in that situation.

Question: Do you agree or disagree with the presence of therapeutic concentrations?

Dr. Schmidt: My position on the question of what constitutes a therapeutic concentration is that there is only one individual effective concentration, and that effective concentration may be defined as the one which causes the patient to have no more seizures. This varies with the seizure type. If you have a patient with generalized tonic-clonic seizures, the patient needs less drug, or a lower concentration of the drug, than a patient with complex partial seizures. We do not know about the limits of therapeutic concentrations in relation to two- or three-drug therapy. Nobody has ever carefully looked at this. We are always extrapolating data from single-drug therapy to multiple-drug therapy. That may not be correct, and may introduce error.

Secondly, the therapeutic concentration that was effective in preventing further seizures at the onset of epilepsy, in the first 6 months or 8 months, is not necessarily the one needed to maintain seizure control a year later. One finds that the effective plasma concentration for an individual changes, and the only way that one can monitor this very crudely, I admit is by reducing the medication and then seeing whether the patient has more seizures. Most physicians shy away from such a drastic litmus test, and keep the patient, if control is maintained for two years, on the same medication. Again, there are no good data on this aspect.