PANEL DISCUSSION

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Question: When a patient is receiving combination antiepileptic drug therapy and you take him or her off one of the drugs, how long is it before you can expect drug levels of the remaining drug to rise because of the effects of disinduction?

Dr. Schmidt: That depends on the type of drug. For example, with the carbamazepine-valproate combination, if you take the patient off carbamazepine, it may take 10 to 30 days for maximum valproate levels to be reached, if morning trough levels are measured. With other combinations, the effect of disinduction is less extensive. We have observed that with phenytoin-carbamazepine, the effect takes eight to ten days.

Dr. Dodson: One has to allow time for the enzyme systems to readjust; earlier work on induction suggests that that process may take several weeks. Once disinduction, or the change in hepatic metabolizing capacity, has occurred, one has to allow sufficient time for the drug to re-equilibrate at steady state. The overall process may be surprisingly longer than one would think just on the basis of the half-lives of the drugs.

Question: Can lorazepam be used in the treatment of neonatal seizures?

Dr. Painter: A pilot study has been conducted on the use of lorazepam in this indication. At dosages of 0.05 to 0.10 mg/kg, it has been efficacious. But the problem is "efficacious" in comparison to what? There have been few controlled studies. For the most part, lorazepam has been used as an adjunctive agent.

Question: Can you explain the biphasic response relationship reported by O'Dougherty for carbamazepine's effect on cognitive function?

Dr. Trimble: If one pushes the level of any drug high enough, the patient will develop relative impairments. Our data in adults show, for instance, that at lower serum levels of sodium valproate or carbamazepine, there is little effect on cognitive function. As dosage rises toward the so-called upper limits of the therapeutic range, one begins to perceive impairments with sodium valproate but not with carbamazepine. Of course, if dosage rises beyond this point, one finds that impairments may develop with any anticonvulsant.

Question: Does prior exposure to valproate sodium in utero alter the half-life of the drug in the newborn period?

Dr. Dodson: There is little evidence that exposure to valproate in utero alters or induces metabolism, but the drug has other consequences. For example, the incidence of hyperbilirubinemia is greater among newborns who are exposed to valproate in utero than among youngsters who are exposed to other drugs. Other antiepileptic drugs induce a variety of hepatic functions, including the ability to conjugate bilirubin. Valproate does not.

Question: Is the prolonged half-life of valproic acid in the newborn period due to beta-oxidation or glucuronidation?

Dr. Dodson: The question relates to the cause or the relative activity of various pathways in valproate elimination that are associated with modification. Presumably, the relative tardiness of valproate elimination is due to defective glucuronidation. A large percentage of valproate metabolites in older youngsters are, in fact, conjugated to glucuronides.

Question: Can carnitine be used to reduce the side effects of valproate and a ketogenic diet?

Dr. Schmidt: In Europe, carnitine is used for this

purpose; and several drug companies are promoting its use. Carnitine in high dosages has been given to children when impending hepatic failure was detected, and in several cases had no apparent effect on the downhill course. The routine use of supplementary carnitine in all children receiving valproate does not seem to have any basis. No data show that this is a means of reducing the toxicity of valproate. I personally have no experience with a ketogenic diet and valproate; but I would think that, if a ketogenic diet induces and changes fatty acid metabolism, there may be a risk of interaction.

Dr. Pippenger: We just had a case of ketogenic diet-induced pancreatitis, with elevated amylases and lipases. That was without valproic acid. You would expect, therefore, that the two together would get you into deeper trouble.

Question: What is the usefulness of carbamazepine in liquid form and of valproic acid in neonatal seizures refractory to other anticonvulsants?

Dr. Painter: Carbamazepine has been advocated because it was felt that one would get therapeutic plasma levels after a lower oral loading dose. In actual fact, when you look at the few infants who have been studied in that regard, the maintenance dosages for carbamazepine are quite comparable to those for phenytoin. There is a wide variability. On a milligram-per-kilogram basis, one goes to 18 to 20 milligrams/kilogram/day to maintain plasma levels. Carbamazepine was the drug implicated in a study in which two infants developed signs of necrotizing enterocolitis. That is a concern in the use of that agent via the oral route. I do not think it is going to help us out of the difficulty we have with our inability to maintain plasma levels in a predictable way with phenytoin.

The use of valproic acid is part of the British collaborative study of neonatal seizures. From preliminary data, it would appear that it is not all that much better than, or is equal to, phenobarbital. I am a bit concerned about using valproic acid in neonates until we better understand the mechanism of valproic acid hepatotoxicity. Because of immature enzyme systems, or perhaps decreased body contents of trace elements that may be implicated in valproic acid toxicity, or because of the oxygen free radical scavenging enzyme levels that may be decreased in neonates, I think the use of the drug in neonates is a bit suspect.

Question: Has anyone looked at changes in cognitive function in newly presenting patients after the administration of antiepileptic drugs?

Dr. Trimble: That has not been done in children, although in adults it has been done by two groups: in the V.A. study in this country and in a study by Reynolds and his group at King's College Hospital in London. Reynolds compared patients receiving monotherapy with carbamazepine or phenytoin and showed significant differences between the two drugs, most of the differences favoring carbamazepine. Carbamazepine adversely affected performance of some motor tasks.

The V.A. cooperative study compared patients on monotherapy with primidone, phenobarbital, phenytoin, or carbamazepine. Differences were noted in the behavioral toxicity profile; carbamazepine came out best, and phenytoin came out worst, with phenobarbital in the middle.

Question: This is a yes-or-no question, gentlemen, with no elaboration. Have you also seen the cognitive difficulties in your patients receiving phenytoin as were described by Dr. Trimble?

Dr. Painter: Yes.

Dr. Schmidt: Yes, high doses.

Dr. Dodson: Yes.

Question: Does phenytoin cause cardiac arrhythmias during or after infusion, or both?

Dr. Painter: In our experience, it has been both.

Dr. Pippenger: I would remind everyone that any drug which contains propylene glycol as a vehicle and is pushed rapidly has the potential to produce arrhythmias.

Question: Has it been proved that phenytoin causes cerebellar atrophy? Might the atrophy not be caused by neuronal hyperactivity, as has been shown with scan studies?

Dr. Schmidt: There is no evidence that phenytoin alone causes cerebellar atrophy. From anecdotal reports, there is suggestive evidence that a number of patients who developed irreversible cerebellar damage during phenytoin therapy had already demonstrated prolonged clinical drug toxicity (nystagmus, ataxia) associated with phenytoin. This is the best evidence to link phenytoin to cerebellar atrophy. My personal belief is that cerebellar atrophy is not related to phenytoin at all. I believe it is associated with the epilepsy of the patient. There is no evidence that phenytoin is related causally, but there are a few cases with findings suggestive of this. Remember, too, that it is easy to avoid chronic phenytoin toxicity. It is

worthwhile, from a practical point of view, to avoid any chronic drug toxicity.

Question: Is valproate-related hyperammonemia related to the omega-pathway metabolism? Or does it represent nonspecific general hepatic dysfunction? Is it related to hepatic failure?

Dr. Dodson: It is believed that valproate-mediated hyperammonemia is a consequence of elevated intramitochondrial concentrations of valproyl CoA. Valproic acid is seen by the liver as a fatty acid substrate for oxidation, and it does several things to fatty acid metabolism in the liver. A major effect which interferes with the metabolism of other fatty acids is that valproic acid consumes and seems to deplete acetyl CoA. Nonetheless, hyperammonemia seems to occur associated with valproic acid, because of the production of valproyl CoA, which inhibits the production of N-acetylglutamine. N-acetylglutamine is a cofactor that regulates the enzyme carbamyl phosphate synthetase. That is the same mechanism that causes hyperammonemia and other organic acidemias.

Question: Conduct disorder was found in a high percentage of the patients discussed by Dr. Trimble. Is this the same as the attention-deficit disorder in the United States?

Dr. Trimble: No, I do not think it is. Conduct disorder is to be seen in the aggressive, somewhat overactive but not hyperactive, destructive, naughty, usually male child. This kind of behavior disorder is one which I am not infrequently presented with in epilepsy. Very often, you can produce a magical change of that child by simply taking him off phenobarbital. Attention-deficit disorder refers more to inattention, impulsivity and hyperactivity, and is classified separately from conduct disorder in DSMIIIR.

Question: Why does phenytoin not achieve therapeutic levels in neonates? Metabolism or absorption?

Dr. Painter: Dodson has evidence that would suggest that the rate of absorption is a determining factor in achieving plasma phenytoin levels, and that, because of relatively slow absorption in the neonate, plasma levels are not maintained. In 1978, we reported that in neonates we could not maintain levels of phenytoin with oral dosage of 10 to 12 milligrams per kilogram per day, either as suspension, IV preparation, or as a tablet (crushed). We questioned whether the drug was predictably absorbed.

The pharmacokinetic principles that Dodson enumerated explained to a certain extent why one could not maintain plasma levels in neonates, despite good absorption. We then looked at the problem with a stable isotope during chronic therapy. Indeed, in the aqueous microcrystalline form in which the isotope was administered, phenytoin showed a very nice absorption curve. With that absorption curve, we really could not explain why we then could not maintain plasma levels.

We are now in the process of replacing background pool activity with the stable isotope and looking at pulse-dosing the suspension in tablet and aqueous preparations to see if there is a difference relative to the absorption of different preparations. On the basis of very preliminary data, it appears that there is, and that in the neonate the tablet is more slowly absorbed than is the suspension.

Question: Can valproate hepatotoxicity be anticipated? Can the process be stopped once it has started? What is the incidence of hepatotoxicity with other drugs?

Dr. Schmidt: It is very difficult, if not impossible, to anticipate valproate hepatotoxicity. There are no reliable indicators from laboratory measurements that allow one to predict hepatic coma, for two reasons. First, approximately 20% to 30% of patients exposed to valproate will develop laboratory evidence of mildly increased transaminase levels. If all patients identified as having developed hepatic coma are looked at retrospectively, in about one-third of the cases there was no laboratory evidence for impending hepatic coma, even at the onset of clinical symptomatology. The only tests predictive of coma are those given when it is immediately impending: namely, when the child has a reduced capacity to produce proteins. By that time, however, it is too late, because the liver has already decompensated.

In most cases, it appears that once the patient truly has hepatic coma, the downhill course cannot be influenced positively. In the literature, there have been two or three reports in which it was maintained that children could be saved from hepatic coma. But if one carefully analyzes the data, some doubt may be entertained as to whether these children truly had hepatic coma.