# A Clinical Study of the Effect of Phenobarbital on Diphenylhydantoin Plasma Levels

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Over 50% of seizure disorders have their onset in childhood.[1] The customary pediatric management is to prescribe phenobarbital as the initial anticonvulsant. If seizure control is not achieved, diphenylhydantoin is added and both drugs are administered concomitantly.[2] However, several authors have pointed out that phenobarbital accelerates the metabolism of diphenylhydantoin by stimulation of the liver's microsomal enzyme system.

Cucinell demonstrated that chronic administration of phenobarbital would accelerate the metabolism of diphenylhydantoin in animals. The half-life of diphenylhydantoin in control dogs averaged 7.3 hours. The half-life of an equivalent dose in dogs pretreated with phenobarbital for 30 days averaged 2.1 hours.[3] In a study of adult epileptic patients, the same authors found that patients receiving diphenylhydantoin and phenobarbital had lower diphenylhydantoin plasma levels than those treated with diphenylhydantoin alone.[4] Buchanan et al. reported that diphenylhydantoin plasma levels in children following a single 10 mg/kg dose were significantly lowered after 30 days of continuous administration of phenobarbital.[5] These results have been confirmed by Kristensen.[6]

These pharmacologic observations suggest that phenobarbital and diphenylhydantoin are an illogical combination although, in fact, they are clinically an excellent combination. Since most of the data are based on animal studies and single-dose human studies, it seemed appropriate to conduct a multiple-dose crossover study in epileptic children to determine whether the pharmacologic observations were truly applicable to clinical pediatric practice. The results are described in this report.

## Method

Twenty patients ranging in age from six to 17 years and in weight from 44 to 122 pounds were selected for this study. All were institutionalized children suffering from mental retardation. All had a known convulsive disorder for at least six months before entering the study. The protocol also required that each participant be on a stable anticonvulsant regime with no drug or dosage change for three months before entering the study. They were then divided into two similar groups: those normally re-

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ceiving only diphenylhydantoin (Dilantin*) and those receiving diphenylhydantoin and phenobarbital. Venous blood specimens were obtained for diphenylhydantoin assay approximately two hours after the morning dose at weekly intervals for a four-week period. Previous studies have shown that diphenylhydantoin is well absorbed two hours after oral dosage.[7]

At the end of four weeks, phenobarbital was added to the medication regime of the patients previously receiving only diphenylhydantoin. Those receiving both medications during the first four-week period had their phenobarbital discontinued. The diphenylhydantoin dose remained unchanged for all patients. Blood specimens for diphenylhydantoin assay were obtained for a second four-week period according to the same schedule as before. Thus, each participant served as his own control in this crossover design. Clinical observations were made during the study to record the number and duration of any seizures.

The assays were performed in the laboratory of Dr. Carl E. Moyer, Department of Clinical Investigation, Parke, Davis & Company, using the colorimetric technique of Dill et al.[7] This method is highly specific for diphenylhydantoin and measures only free drug without interference from metabolites or phenobarbital. It was selected because phenobarbital is known to interfere with other diphenylhydantoin assay techniques.[8]

## Results

Table I illustrates the diphenylhydantoin plasma assays for the participants who received only diphenylhydantoin before and during the first phase of the study and diphenylhydantoin and phenobarbital during the second phase. The average value is given for each participant and for all the participants for each of the two phases. Table II gives the same information for the participants who were receiving diphenylhydantoin and phenobarbital before and during the first phase of the study and diphenylhydantoin alone during the second phase.

The participants receiving diphenylhydantoin alone during the first phase (Table I) had an average assay of 3.1 $\mu$g/ml, and after the addition of phenobarbital the average assay was 3.0 $\mu$g/ml. If phenobarbital stimulated the metabolism of diphenylhydantoin a significant decrease would be expected, but this did not occur. There is no significant difference between these values ($P<0.01$). The mean diphenylhydantoin dose for the patients described in Table I was 3.3 mg/kg/day.

The participants receiving diphenylhydantoin and phenobarbital during the first phase (Table II) had an average assay of 6.4 $\mu$g/ml. After phenobarbital was stopped, the diphenylhydantoin assay would be expected to increase. However, it fell to 6.1 $\mu$g/ml. Again, there is no significant difference ($P<0.01$). The mean diphenylhydantoin dose for this group was 4.2 mg/kg/day.

Table III lists the age, weight, and drug dosage for each of the participants. Each received phenobarbital during only one of the two study phases, as indicated in Tables I and II.

## Discussion

This study fails to demonstrate any stimulation of diphenylhydantoin metabolism by phenobarbital when the plasma assays are followed over a two-month controlled period. This observation correlates well with the customary usage, in which the drugs are prescribed together for greater seizure control. A previous multiple-dose pediatric study also indicated phenobarbital may not stimulate diphenylhydantoin metabolism.[9]

* Registered trade name, Parke, Davis & Co.

## TABLE I

**Patients Receiving Diphenylhydantoin Alone Weeks 1 through 4, Diphenylhydantoin with Phenobarbital Weeks 5 through 8**

Diphenylhydantoin Plasma Concentration Micrograms/Milliliter

| Week no. | Patient number | | | | | | | | | | Average value |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | 1 | 4 | 6 | 7 | 10 | 12 | 14 | 17 | 18 | 19 | |
| 1 | 2.7 | 3.6 | 2.6 | 0.8 | 2.4 | 6.1 | 1.2[a] | 7.1 | 0.2 | 4.1 | 3.1 |
| 2 | 1.2 | 3.2 | 3.4 | 1.9 | 3.0 | 6.3 | 2.0 | 7.9[b] | 0.8 | 5.4 | 3.5 |
| 3 | 1.1 | 4.4 | 4.3[c] | 1.1 | 3.4 | 5.4 | 0.9 | 4.0 | 0.8 | 4.1 | 2.8 |
| 4 | 1.3 | 4.8 | 3.2 | None | 1.3 | 6.6 | 1.8 | 8.5 | 0.5 | 4.1 | 2.9 |
| Average value | 1.6 | 4.0 | 3.4 | 1.0 | 2.5 | 6.1 | 1.5 | 7.5 | 0.6 | 4.4 | 3.1 |
| 5 | 0.3 | 3.4 | 3.8 | 0.6 | 1.4[d] | 4.4 | 0.2 | 12.1 | 0.7 | 4.5 | 3.1 |
| 6 | 1.4 | 2.9 | 3.2 | 0.7 | 1.5 | 4.5 | 1.8 | 8.0 | 1.5 | 5.1 | 3.2 |
| 7 | 0.8 | 2.6 | 4.4 | 1.9 | 2.7 | 5.4 | 1.8 | 5.6 | 1.3 | 6.3 | 3.3 |
| 8 | 0.1 | 3.6 | 2.8 | 0.4 | 2.1 | 4.4 | 1.2 | 10.6 | 1.0 | 7.6 | 3.5 |
| Average value | 0.7 | 3.1 | 3.5 | 0.9 | 2.1 | 4.7 | 1.3 | 8.1 | 1.1 | 5.9 | 3.0 |

[a] One seizure before medication change.

[b] One seizure before medication change. Phenobarbital added Wk. 3 and continued.

[c] One seizure before medication change. Phenobarbital added Wk. 4 and continued.

[d] Phenobarbital added Wk. 5 only.

## TABLE II

**Patients Receiving Diphenylhydantoin with Phenobarbital Weeks 1 through 4, Diphenylhydantoin Alone Weeks 5 through 8**

Diphenylhydantoin Plasma Concentration Micrograms/Milliliter

| Week no. | Patient number | | | | | | | | Average value |
|---|---|---|---|---|---|---|---|---|---|
| | 2 | 3 | 5 | 8 | 9 | 11 | 15 | 20 | |
| 1 | 2.3 | 12.6 | 4.8 | 4.1 | 5.0 | 3.2 | 5.3 | 12.8 | 6.4 |
| 2 | 0.3 | 6.7 | 25.1 | 9.3 | 0.1 | 0.4 | 0.8 | 21.3 | 9.0 |
| 3 | 1.6 | 15.3 | 7.1 | 8.1 | 8.4 | 8.9 | 10.9 | 13.8 | 9.0 |
| 4 | 1.4 | 11.8 | 4.8 | 8.4 | 7.7 | 3.6 | 5.6 | 14.5 | 7.5 |
| Average value | 1.4 | 11.6 | 10.5 | 7.0 | 5.3 | 4.0 | 5.7 | 15.6 | 6.4 |
| 5 | 1.5 | 12.3 | 5.2 | 9.9 | 7.4 | 1.2 | 3.3[a] | 11.0 | 6.9 |
| 6 | 2.3 | 9.4 | 6.6 | 6.7 | 5.6 | 2.9 | 5.5 | 8.2 | 6.0 |
| 7 | 2.2 | 10.5 | 5.0 | 6.6 | 2.5 | 2.8 | 6.3 | 12.2 | 6.0 |
| 8 | None | 10.2 | 5.5 | 8.0 | 3.6 | 4.4 | 7.2 | 11.0 | 7.1 |
| Average value | 2.0 | 10.6 | 4.3 | 7.6 | 4.8 | 2.8 | 6.3 | 10.6 | 6.1 |

[a] Four seizures in one day (**five days after** medication change). Phenobarbital resumed and continued.

One possible explanation for the difference between the previously described single-dose studies and the results of this multiple-dose study is that the stimulation of diphenylhydantoin metabolism is a short-term or transient phenomenon of perhaps only a few days' duration. Much remains unknown about the liver's microsomal enzyme systems. Perhaps studying diphenylhydantoin levels more frequently after the addition or removal of phenobarbital would provide further information.

The diphenylhydantoin plasma assays fluctuate through a moderately wide range. Loeser has described this same variation in studies of clinic patients.[10] These assay results also appear lower than the usual therapeutic range of 10 μg/ml described by Buchtal et al.[11] A partial explanation may be that the highly specific Dill and Glazko analytic method was used to exclude any interference by phenobarbital.[8]

Essentially, no difference in seizure control was noted. Livingston has previously indicated that the stimulating effect of phenobarbital on diphenylhydantoin metabolism has no influence on seizure control.[2] Only participant No. 16 had to be placed back on phenobarbital during the study, as illustrated in Table II. Understandably, because of the medication manipulation, patients usually under good seizure control were selected for this study. This selection may also have contributed to the low drug levels noted, more severely affected patients being excluded. The mean diphenylhydantoin dose for all patients was 3.7 mg/kg/day.

## Summary

This longitudinal crossover study fails to demonstrate any significant stimulation of diphenylhydantoin metabolism by phenobarbital. No adverse effect on seizure control was noted.

**TABLE III**

| Patient no. | Age (years) | Weight (kg) | Diphenylhydantoin mg/kg/day | Phenobarbital[a] mg/kg/day |
|---|---|---|---|---|
| 1 | 15 | 40 | 1.5 | 1.0 |
| 2 | 6 | 20 | 3.0 | 1.5 |
| 3 | 10 | 30 | 6.7 | 2.0 |
| 4 | 12 | 24 | 3.0 | 0.75 |
| 5 | 14 | 55 | 4.5 | 1.2 |
| 6 | 13 | 33 | 6.0 | 4.0 |
| 7 | 15 | 38 | 1.0 | 0.75 |
| 8 | 10 | 24 | 4.0 | 1.2 |
| 9 | 12 | 31 | 3.0 | 6.6 |
| 10 | 13 | 31 | 3.0 | — |
| 11 | 17 | 34 | 3.0 | 1.0 |
| 12 | 14 | 38 | 5.3 | 0.75 |
| 14 | 12 | 31 | 2.0 | 1.0 |
| 15 | 12 | 20 | 5.0 | 3.0 |
| 17 | 11 | 30 | 3.3 | 2.0 |
| 18 | 14 | 34 | 2.0 | 1.0 |
| 19 | 12 | 24 | 5.4 | 2.5 |
| 20 | 10 | 20 | 5.0 | 1.5 |

[a] Phenobarbital administered to each patient for half of the study period only.

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