

REFERENCES

- Abbott, TDX FSE Training. Diagnostic Division, Abbott Laboratories, North Chicago, IL 60064
- Bauer, L.A., and Blouin, R.A. 1983. Phenytoin Michaelis-Menten Pharmacokinetics in Caucasian Paediatric Patients. Clinical Pharmacokinetics. 8: 545-549.
- Berg, M.J., Ebert, B.E., Fincham, R.W., and Schottelius, D.D. 1987. Phenytoin Binding in Healthy Volunteers. Therapeutic Drug Monitoring. 9: 384-388.
- Cai, W.M., Zhu, G.Z., and Chen, G. 1993. Free Phenytoin Monitoring in Serum and Saliva of Epileptic Patients in China. Therapeutic Drug Monitoring. 15: 31-34.
- Chapron, D.J., LaPierre, B.A., and Elkair, M.A. 1993. Unmasking the significant enzyme inducing effects of phenytoin on serum carbamazepine concentrations during phenytoin withdrawal. The Annals of Pharmacotherapy. 27: 708-711.
- Evans, W.E., Schentag, J.J., and Jusko, W.J., eds. 1986. Phenytoin. Applied Pharmacokinetics : Principles of Therapeutic Drug Monitoring. 2nd ed. USA.
- Evens, R.P., Fraser, D.G., Ludden, T.M., and Sutherland, E.W. 1980. Phenytoin Toxicity and Blood Levels after a Large Oral Dose. American Journal of Hospital Pharmacy. 37: 232-235.
- Faingold, C.L., and Fromm, G.H. 1992. Drugs for Control of Epilepsy: Actions on Neuronal Networks Involved in Seizure Disorders. USA.
- Hayes, G and Kootsikis, M.E. 1993. Reassessing the lower end of the phenytoin therapeutic range: a review of the literature. The Annals of Pharmacotherapy. 27: 1389-1392.

- Houghton, G.W., Richens, A., Leighton, M. 1975. Effect of age, height, weight, and sex on serum phenytoin concentration in epileptic patients. Br. J. Clin. Pharmacol. 2:251-256.
- Hudson, S.A., and Walker, R.W. 1990. Pharmaceutical Practice. Newyork: Churchill Livingstone.
- Hull, R.L. 1993. Possible phenytoin-ciprofloxacin interaction. The Annals of Pharmacotherapy. 27: 1283.
- Inoue, F, and Kolabinski, I. 1986. Possible Interaction Between Phenytoin Therapy and Folate Supplement - Two Case Reports. The Canadian Journal of Hospital Pharmacy. 39: 16-18.
- Jolly, M.E., Stroupe, S.D., Schwenger, K.S., and et al. 1981. Fluorescence polarization immunoassay III. an automated system for therapeutic drug determination. Clin. Chem. 21(7) : 1575-1579.
- Ludden, T.M., and others. 1976. Individualization of phenytoin dosage regimens. Clinical Pharmacokinetic and Therapeutic. 11: 287-293.
- Lund, L. 1974. Anticonvulsant Effect of Diphenylhydantoin Relative to Plasma Levels. Archive of Neurology. 31: 289-294.
- Martin, E., Tozer, T.N., Sheiner, L.B., and Riegelman, S. 1977. The Clinical Pharmacokinetics of Phenytoin. Journal of Pharmacokinetics and Biopharmaceutics. 5: 579-596.
- Perlik, F., Kolinova, M., Zvarova, J., and Patzelova, V. 1995. Phenytoin as a Risk Factor in Gingival Hyperplasia. Therapeutic Drug Monitoring. 17: 445-448.
- Peterson, G.M., Khoo, B.H.C., and Witt, R.J. 1991. Clinical Response in Epilepsy in Relation to Total and Free Serum Levels of Phenytoin. Therapeutic Drug Monitoring. 13: 415-419.

- Sadee, W., and Beelen, G.C.M. 1980. Drug Monographs:phenytoin. Drug Level Monitoring: Analytical Techniques, Metabolism, and Pharmacokinetics. Canada:John Wiley & Sons, Inc.
- Salem, R.B., Wilder, B.J.,Yost, R.L., Doering, P.L., and Lee, C. 1981. Rapid Infusion of Phenytoin Sodium Loading Doses. American Journal of Hospital Pharmacy. 38 : 354-357.
- Schmidt, D., and Seldon, L. 1982. Phenytoin. Adverse Effects of Antiepileptic Drugs. New York: Raven Press.
- Taylor, W.J., and Diescaviness, M.H., eds. 1986. Phenytoin. A Textbook for the Clinical Application of Therapeutic Drug Monitoring. North Chicago: Abbott Laboratories, Diagnostics Division.
- Ted Tse, C.S., Aldnwande, K.I., and Biallowons, K. 1993. Phenytoin concentration elevation subsequent to ranitidine administration. The Annals of Pharmacotherapy. 27: 1448-1451.
- Ward, A.A., Penry, J.K., and Purpura, D.P. 1983. Adverse effects of antiepileptic drugs. Epilepsy. New York: Raven.
- Wilson, J.F., Tsanaclis, L.M., Williams. J., Tedstone, J.E., and Richens, A. 1989. Evaluation of Assay Techniques for the Measurement of Antiepileptic Drugs in Serum: A study Based on External Quality Assurance Measurements. Therapeutic Drug Monitoring. 11: 185-195.
- Winter, M.E., Katcher, B.S., and Kimble, M. 1980. Phenytoin. Basic Clinical Pharmacokinetics. USA

APPENDICES

APPENDIX I

EXAMPLE OF DATA RECORD FORM

Blood Collection

| | | | | | | | |
|----------------------|-------------|-------------|-------------|-------------|-------------|-------------|-------------|
| Blood Collected | .../.../... | .../.../... | .../.../... | .../.../... | .../.../... | .../.../... | .../.../... |
| Time take phnytoin | | | | | | | |
| Time collected blood | | | | | | | |
| Time assayed | | | | | | | |
| | | | | | | | |
| | | | | | | | |

Alcohol Drinking History

Drank yr. Alcohol cup/d

Stop drank yr.

Drinking yr. Alcohol cup/d

Smoking History

Smoked yr. Cigarette /d

Stop smoking yr.

Smoking yr. Cigarette /d

Drug Allergy History

.....

Other Data

Other drugs out of this hospital

.....

.....

APPENDIX II

EXAMPLE OF EQUATIONS

Equations used for calculation of phenytoin pharmacokinetic parameter and serum concentrations

$$\text{Equation 1 : Loading dose} = \frac{Vd \cdot Cp}{S \cdot F} = \frac{Vd(Cp_{\text{desired}} - Cp_{\text{initial}})}{S \cdot F}$$

$$\text{Equation 2 : Maintenance dose} = \frac{(Vm)(Cpss)(T)}{(Km + Cpss)(S)(F)}$$

$$\text{Equation 3 : } Cp = \frac{Km \times (S)(F)(DOSE/T)}{Vm - (S)(F)(DOSE/T)}$$

Equation 4 : When serum albumin was low

$$Cp_{\text{adjusted}} = \frac{Cp}{0.2 \times \text{alb.} + 0.1}$$

Equation 5 : When renal failure and serum albumin was low

$$Cp_{\text{adjusted}} = \frac{Cp}{0.1 \times \text{alb.} + 0.1}$$

Equation 6 : Wagner methods

$$\ln Cp_{\text{wag}} = \ln Cp_1 + \ln b \cdot (DOSE_2 - DOSE_1)$$

$$b = 1.0078025$$

Vd = Volume of Distribution (L/kg)

Cp = Measured Serum Phenytoin Concentration (µg/mL)

S = Sodium Salt (0.92)

F = Bioavailability (1.0)

DOSE = Phenytoin Dose (mg/d)

T = Dosing Interval (d)

alb. = Serum Albumin

K_m = Michaelis constant (μg/mL)

V_{max} = The Maximum Rate of Metabolism (mg/kg/d)

When phenytoin used with other drug , calculated by equation and corection factors (Q) as followed :

$$\text{Dose(adjusted)} = \text{Dose (observed)}/Q$$

$$C_p \text{ of Phenytoin + Drug} = C_p \text{ of Phenytoin} \times Q$$

Correction factor (Q) :

| | |
|-----------------------------|-----------------------|
| Amiodarone | 2.58 |
| Benzodiazepines | 1.84 |
| Carbamazepine | 0.87 |
| Carbamazepine+Phenobarbital | 0.80 |
| Chloramphenicol | 3.91 |
| Cimetidine | 3.91 |
| Contraceptives | 1.34 |
| Folic acid | 0.73 |
| Isoniazid | 2.71 |
| Metronidazole | 1.18 |
| Phenobarbital | 0.94 |
| Pyridoxine | 0.65 |
| Salicylate | 0.84 |
| Tolbutamide | 0.91 |
| Valproic acid | 0.75 (5-10 weeks) |
| | 0.93 (after 6 months) |

APPENDIX III

Details of Clinical Responses in Patients

Clinical Responses of Patients Receiving Phenytoin.

| Pt. No. | Dose/d (mg.) | Duration of Epileptic treatment (yr.) | Duration of Phenytoin treatment (yr.) | Frequency of seizure (/month) | Duration of seizure (min.) | Clinical response | | | Adverse Reactions |
|---------|-----------------|--|--|----------------------------------|-------------------------------|-------------------|-----------|-------------|--|
| | | | | | | Absolutely | Partially | Not control | |
| 1 | 300 | 2 | 2 | No seizure | No seizure | / | | | horizontal nystagmus, gum hypertrophy, drowsiness |
| 2 | 300 | 17 | 13 | 3-4 | 0.5 | | / | | gum hypertrophy |
| 3 | 350 | 7 | 6 | 2-3 | 1 | | / | | |
| 4 | 400 | 1 | 1 | 3 | 1 | | | / | Ataxia, Diplopia, Dizziness |
| | 300 | | | 3 | 1 | | | / | |
| 5 | 300 | 27 | 7 | 1 | 1 | | / | | |
| 6 | 350 | 20 | 8 | 2-3 | 1 | | | / | mild horizontal nystagmus |
| 7 | 300 | 18 | 3 | 2 | 2-3 | | / | | mild gaze horizontal nystagmus |
| 8 | 300 | 26 | 10 | 4-5 | 1-2 | | / | | gum hypertrophy |
| | 350 | | | 1-2 | 0.5 | | / | | gum hypertrophy |
| 9 | 300 | 30 | 12 | 1-2 | 1 | | | / | |
| 10 | 400 | 23 | 6 | 1-2 | 0.5 | | / | | |

Continue....

| Pt. No. | Dose/d (mg.) | Duration of Epileptic treatment (yr.) | Duration of Phenytoin treatment (yr.) | Frequency of seizure (/month) | Duration of seizure (min.) | Clinical response | | | Adverse Reactions |
|---------|-----------------|--|--|----------------------------------|-------------------------------|-------------------|-----------|-------------|-------------------------------------|
| | | | | | | Absolutely | Partially | Not control | |
| 11 | 300 | 30 | 5 | No seizure | No seizure | / | | | horizontal nystagmus |
| 12 | 300 | 25 | 23 | 1-2 | 1 | | / | | |
| | 350 | | | No seizure | No seizure | / | | | |
| 13 | 250 | 29 | 8 | 2-3 | 1 | | / | | gum hypertrophy |
| 14 | 300 | 27 | 10 | >10 | 5 | | | / | gum hypertrophy, headache |
| 15 | 300 | 8 | 8 | 2-3 | 3 | | / | | gum hypertrophy, drowsiness |
| 16 | 300 | 19 | 19 | 1 | 1 | | / | | gaze horizontal nystagmus |
| 17 | 300 | 17 | 16 | No seizure | No seizure | / | | | nystagmus |
| 18 | 300 | 10 | 8 | 1-2 | 1 | | / | | |
| 19 | 300 | 19 | 2 | 1 | 5 | | / | | |
| 20 | 300 | 8 | 8 | No seizure | No seizure | / | | | nystagmus, gum hypertrophy |
| 21 | 300 | 43 | 4 | No seizure | No seizure | / | | | gum hypertrophy |
| 22 | 300 | 10 | 10 | 1-2 | 0.5 | | / | | mild nystagmus |
| 23 | 200 | 16 | 14 | 0.5 | 0.5 | | / | | gum hypertrophy |
| | 300 | | | No seizure | No seizure | / | | | gum hypertrophy, acne drowsiness |

Continue....

| Pt. No. | Dose/d (mg.) | Duration of Epileptic treatment (yr.) | Duration of Phenytoin treatment (yr.) | Frequency of seizure (/month) | Duration of seizure (min.) | Clinical response | | | Adverse Reactions |
|---------|-----------------|--|--|----------------------------------|-------------------------------|-------------------|-----------|-------------|--|
| | | | | | | Absolutely | Partially | Not control | |
| 24 | 200 | 5 | 5 | 1-2 | 5 | | / | | |
| | 250 | | | No seizure | No seizure | / | | | drowsiness |
| | 300 | | | No seizure | No seizure | / | | | drowsiness |
| 25 | 350 | 16 | 5 | 5-6 | 2-3 | | | / | |
| 26 | 300 | 31 | 0.66 | 1-2 | 5-10 | | / | | |
| | 350 | | | 1-2 | 0.5 | | / | | |
| | 400 | | | No seizure | No seizure | / | | | |
| 27 | 400 | 7 | 3 | 5 | 5 | | | / | |
| 28 | 350 | 17 | 17 | 3 | 1 | | / | | drowsiness |
| 29 | 300 | 39 | 10 | 2 | 1 | | / | | drowsiness |
| 30 | 300 | 16 | 4 | 5-6 | 2-3 | | | / | nystagmus |
| 31 | 300 | 12 | 12 | 3 | 0.5 | | / | | gum hypertrophy |
| 32 | 300 | 24 | 11 | >10 | 5 | | | / | gum hypertrophy |
| 33 | 175 | 6 | 6 | No seizure | No seizure | / | | | dizziness |
| 34 | 300 | 46 | 10 | 1-2 | 0.5 | | / | | horizontal nystagmus, gum hypertrophy |

Continue...

| Pt. No. | Dose/d (mg.) | Duration of Epileptic treatment (yr.) | Duration of Phenytoin treatment (yr.) | Frequency of seizure (/month) | Duration of seizure (min.) | Clinical response | | | Adverse Reactions |
|---------|-----------------|--|--|----------------------------------|-------------------------------|-------------------|-----------|-------------|--|
| | | | | | | Absolutely | Partially | Not control | |
| 35 | 300 | 10 | 10 | 2 | 0.5 | / | | | nystagmus, ataxia, dizziness |
| 36 | 350 | 29 | 26 | 1 | 0.5 | / | | | gum hypertrophy, drowsiness |
| 37 | 250 | 6 | 5 | 2 | 5 | | | / | gum hypertrophy |
| 38 | 300 | 16 | 8 | 7-8 | 2-3 | | | / | |
| 39 | 300 | 26 | 13 | 1 | 0.5 | / | | | gum hypertrophy |
| 40 | 300 | 9 | 4 | 1-2 | 0.5 | / | | | gum hypertrophy |
| | 400 | | | 1 | 0.5 | / | | | gum hypertrophy, dizziness |
| 41 | 300 | 20 | 18 | 2 | 0.5 | / | | | gum hypertrophy |
| 42 | 300 | 25 | 5 | 1 | 1-2 | / | | | gum hypertrophy |
| 43 | 300 | 24 | 8 | 3-4 | 5 | | | / | gum hypertrophy |
| 44 | 300 | 6 | 6 | 1 | 0.5 | / | | | |
| 45 | 300 | 6 | 6 | No seizure | No seizure | / | | | nystagmus, ataxia, nausea, vomiting, headache |
| | 200 | | | No seizure | No seizure | / | | | |
| 46 | 200 | 1 | 1 | No seizure | No seizure | / | | | |
| 47 | 300 | 1 | 1 | 1-2/d | 0.5 | / | | | |
| 48 | 300 | 24 | 14 | 1-2/d | 0.5-1 | | | / | cerebellar atrophy |

Continue....

| Pt. No. | Dose/d (mg.) | Duration of Epileptic treatment (yr.) | Duration of Phenytoin treatment (yr.) | Frequency of seizure (/month) | Duration of seizure (min.) | Clinical response | | |
|---------|-----------------|--|--|----------------------------------|-------------------------------|-------------------|-----------|---|
| | | | | | | Absolutely | Partially | Not control |
| 49 | 325 | 36 | 30 | No seizure | No seizure | / | | |
| 50 | 300 | 4 | 4 | No seizure | No seizure | / | | nystagmus, ataxia, nausea, vomitting |
| | 250 | | | No seizure | No seizure | / | | |
| 51 | 100 | 3 | 3 | 1-2/d | 0.5-1 | | / | |
| 52 | 300 | 4 | 4 | 1-2/d | 1 | | / | horizontal nystagmus, ataxia |
| | 200 | | | 0-1/d | 0.5 | | / | |
| 53 | 50 | 0.16 | 0.16 | 1-6/d | 0.5-1 | | / | |
| 54 | 200 | 4 | 4 | No seizure | No seizure | / | | |

VITA

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