CHAPTER II

REVIEW OF LITERATURE

Review of Phenytoin

1. Chemistry

Phenytoin is 2,4-Imidazolidinedione, 5,5-diphenylhydantoin or 5,5-Diphenylhydantoin [57-41-0] $C15H_{12}N_2O_2$(252.27). Practically insoluble in water ; slightly soluble in cold alcohol, chloroform or ether.

Phenytoin sodium is 2,4-Imidazolidinedione, 5,5-diphenyl-, monosodium salt or 5,5-Diphenylhydantoin sodium salt [630-93-3] $C_{15}H_{11}N_2NaO_2$(274.25). Freely soluble in water, the solution usually being somewhat turbid due to partial hydrolysis and absorption of carbondioxide, soluble in alcohol, partially insoluble in ether or chloroform .

2. Pharmacology

Mechanism of action

Phenytoin blocks post-tetanic potentiation (PTP) by influencing synaptic transmission in a variety of ways. These influences include(Taylor and Diescaviness, 1986; Faingold and Fromm, 1992):

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- Alterations in ion fluxes (sodium, potassium, chloride) associated with depolarization, repolarization, and membrane stability.

- Calcium uptake in presynaptic terminals and calcium energy metabolism.

- The sodium-potassium adenosine triphosphatase-dependent ionic membrane pump.

- Cyclic nucleotide build-up.

- Calcium-dependent synaptic protein phosphorylation and transmitter release.

- Cerebellar stimulation.

3. Clinical pharmacokinetics

3.1 Absorption

Phenytoin is almost completely absorbed from the gastrointestinal tract (85% to 95%) when administerd orally as the capsule, chewable tablet, or suspension. Most of the drug is absorbed from the duodenum, with little absorption occuring from the stomach. Some absorption also occurs in the jejunum and ilium. The absorption rate of phenytoin is greatly influenced by dosage formulation factors such as particle size and excipient, and may also be affected by food intake(Taylor and Diescaviness, 1986).

After oral administration of the capsule or chewable tablet, peak phenytoin concentrations occur within three to 12 hours. A second peak may be observed within eight to 15 hours. secondary peaks may also be observed as a consequence of enterohepatic cycling of phenytoin. The rate of phenytoin absorption is faster for many generic phenytoin preparations than for the Dilantin Kapseal®. Phenytoin absorption may be slower when antacids are administerd concurrently(Taylor and Diescaviness, 1986).

3.2 Distribution

Volume of distribution:

The volume of distribution of phenytoin in patients with normal renal function and serum albumin is approximately 0.6 L/kg and 0.8 L/kg. Phenytoin binds to both serum and tissue proteins to approximately the same extent.

Phenytoin is 69% to 95% bound (average 90% bound) to the albumin fraction of serum proteins. This wide range of unbound phenytoin fractions (0.05 to 0.31) among individuals implies that reference to a therapeutic range of total phenytoin concentrations will be misleading for some patients.

Phenytoin distributes by passive diffusion into body fluids including cerebrospinal fluid, gastrointestinal fluids, saliva, semen, and breast milk. The concentration of phenytoin in saliva and cerebrospinal fluid is similar to the unbound concentration of phenytoin in serum. Because of this, unbound concentrations of phenytoin in serum (or CSF concentrations) can be indirectly estimated by measurement of phenytoin in saliva(Taylor and Diescaviness, 1986 ; Cai, Zhu, Chen, 1993).

3.3 Metabolism and Elimination

Phenytoin is metabolized by the hepatic microsomal mixed-function oxidase system (cytochrome P-450 system). Phenytoin is mainly metabolized to 5-(4-hydrophenyl)-5-phenylhydantoin (4′-OH-phenytoin), which is further glucuronidated and excreted into the urine. The metabolite 4′-OH-phenytoin is optically active. Parahydroxylation of phenytoin is readily saturable at therapeutic doses; therefore a small increase in the phenytoin dose may cause unproportionally large increases of phenytoin serum levels as a complicating factor in its clinical use. The serum elimination half-life of phenytoin shows large interindividual variability

(24±12 hrs). Some patients have an unusually high metabolic clearance of phenytoin(Sadee and Beelen, 1980 ; Faingold and Fromm, 1992).

Clearance:

The clearance of phenytoin from serum occurs primarily by metabolism, and the rate of this drug's metabolism approaches its maximum at therapeutic concentration. Thus, the metabolism of phenytoin is described as being capacity limited. Capacity limited metabolism results in clearance values that decrease with increasing serum concentrations. This implies that as the maintenance dose is increased, the serum concentration rises disproportionately. This disproportionate rise in the steady state serum level makes dosage adjustment difficult (Winter, Katcher and Kimble, 1980).

Half-Life:

Half-life of phenytoin or $t_{50\%}$ averages 22 hours and ranges from 7 to 42 hours. With increasing doses, the $t_{50\%}$ increases and a longer time is required to reach a new steady state. In stitutions of phenytoin overdose, serum phenytoin concentrations will initially decline at slower rates than would be predicted from $t_{50\%}$ reported in patients taking normal doses.

The $t_{50\%}$ of phenytoin may be altered by drugs that affect the body clearance of phenytoin via enzyme induction or inhibition. The $t_{50\%}$ also varies among patient populations. Preterm neonates younger than two weeks have prolonged "half-lifes" because they have larger volume of distribution and incomplete maturation of hepatic enzyme systems. Children between the ages of six months and six years have higher body clearances and shorter elimination "half-lives" than adults. Elderly patients may have lower body clearances than adolescents and adults, and hence, may have longer phenytoin "half-lives"(Taylor and Diescaviness, 1986).

3.4 Pharmacokinetic Parameters

3.4.1 The Michaelis constant (K_m)

The Michaelis constant is the serum phenytoin concentration at which the rate of metabolism is half maximal averages 4 μg/mL, with a range of 1 to 15 μg/mL (Taylor and Diescaviness, 1986).

3.4.2 The maximum rate of metabolism (V_{max})

V_{max} is the maximum rate of metabolism ; in adults averages 7 mg/kg/d, with a range of 1.4 to 14 mg/kg/d (Taylor and Diescaviness, 1986).

The value of V_{max} in children (< six years) is greater than in older children (seven to sixteen years) which is greater than that in adults(Evans, Schentag and Jusko, 1986). Bauer and Blouin (1983) reported that mean V_{max} and K_m values were 13.95 mg/kg/d and 6.59 μg/mL for 0.5 to 3-year-old patients, 10.93 mg/kg/d and 6.82 μg/mL for the 4 to 6 year age group, 10.05 mg/kg/d and 6.51 μg/mL for the 7 to 9-year-olds, and 8.25 mg/kg/d and 5.69 μg/mL for the 10 16 year group(Bauer and Blouin, 1983).

3.5 Factors Affecting Phenytoin Elimination

Disease States:

Renal disease: In patients with renal impairment and uremia, the percentage of phenytoin bound to serum protiens is reduced. This is probably more related to metabolic product inhibition or conformational changes in the albumin molecule than to reduced serum albumin concentrations. As a consequence of the higher unbound fraction of phenytoin in serum, there is a higher clearance of total phenytoin and lower total phenytoin concentrations in serum. However, because there is presumed to be no change in the clearance of unbound

phenytoin (ie, no change in enzyme activity), unbound concentrations of phenytoin are the same in uremics as in nouremics. No change in the daily dose of phenytoin should be required in uremic patients, therefore, despite the observation of lower total concentrations (Taylor and Diescaviness, 1986).

A shorter half-life of phenytoin has been reported in uremic patients. Possible explanations include phenytoin displacement from tissue proteins and/or enhanced hepatic metabolism (increase intrinsic clearance) of phenytoin. Because of the shorter half-life, more frequence dosing of phenytoin may be required in uremic patients to prevent wide fluctuations in serum phenytoin concentrations. If intrinsic clearance is higher in uremics, higher daily doses may also be required(Taylor and Diescaviness, 1986).

Hepatic Disease: Higher than normal unbound fractions of phenytoin may also occur in patients with hepatic disease because of lower than normal concentrations of serum albumin. The decrease in phenytoin binding may also be secondary to elevated concentrations of billirubin. As in the case of patients with renal impairment, antiepileptic efficacy will be observed with total phenytoin concentrations that are lower than the usual therapeutic range.

In severe hepatic failure, the hepatic clearance of unbound phenytoin may also be reduced as a result of hepatic tissue destruction and a reduction in enzyme activity. When this occurs, a reduction in the daily phenytoin dose may be required to keep unbound phenytoin concentrations below a potentially toxic level. It is especially important to recognize in this situation that a total phenytoin concentration that is apparently therapeutic or sub-therapeutic may accually be associated with phenytoin toxicity. Careful monitoring of the patient for efficacy and signs of toxicity is extremely important(Taylor and Diescaviness, 1986).

Age:

Newborns and infants in the first three months of life have higher free fractions of phenytoin in serum due to lower serum albumin concentrations and competition for albumin

binding sites by bilirubin. The therapeutic range of total concentrations will be lower than in older children and adults.

Age related pharmacokinetic differences in the elderly may be due to changes in absorption, body composition, serum protein binding, hepatic enzyme activity, or to changes in renal function(Taylor and Diescaviness, 1986).

Drug Interactions (Taylor and Diescaviness, 1986; Faingold and Fromm, 1992; Ward, Penry, and Purpura, 1983):

- Increases phenytoin serum concentration

Phenobarbital : Phenobarbital has competitive inhibition between phenytoin.

Methosuximide : The primary metabolite of methosuximide competes with phenytoin for metabolic enzymes.

Disulfiram and Sulthiame : Disulfiram and sulthiame inhibit phenytoin metabolism.

Isoniazid : Isoniazid increases phenytoin serum concentrations in about 10% of epileptic patients. Slow acetylators are more likely to exibit this effect.

Chloramphenicol, Bishydroxycoumarin, Cimetidine, and propoxyphene : elevate phenytoin serum concentrations.

Ranitidine : increased phenytoin serum concentration 40% by reducing phenytoin metabolism (Ted Tse, Akinwande, and Biallowons, 1993).

Ciprofloxacin : reduced phenytoin metabolism (Hull, 1993).

- Reduces phenytoin serum concentration

Nicotine : increased metabolism.

Antacids : Antacids may reduce phenytoin absorption.

Phenobarbital, Carbamazepine and chronic ethanol consumption : induce the enzymes involved in phenytoin metabolism.

Valproic acid and Phenylbutazone : inhibit the metabolism of phenytoin and displace phenytoin from albumin binding sites.

Aspirin : increase in the unbound fraction of phenytoin , increase in its clearance, and a reduction in total concentrations.

Benzodiazepines, Phenothiazines, and tricyclic antidepressants are contradictory, no clinically significant interactions are observed.

4. Adverse Drug Reactions

Phenytoin side effects such as hypertrichosis, gingival hypertrophy, thickening of facial features, carbohydrate intolerance, folic acid deficiency, peripheral neuropathy,vitamin D deficiency, osteomalacia, and systemic lupus erythematosus do not appear to be readily related to the serum phenytoin concentration.

Central nervous system side effect such as nystagmus, ataxia, and decreased mentation have been associated with elevated phenytoin concentrations, with the more severe symptoms occuring at higher concentrations. Far-lateral nystagmus occurs in the majority of patients with concentrations exceeding 20 μg/mL, and nystagmus at a 45-degree lateral gaze, as well as ataxia, usually occurs with concentrations exceeding 30 μg/mL. Significantly diminished mental capacity and ataxia are usaually apparent when phenytoin concentrations are above 40 μg/L. Mild side effects initially appeared at serum concentrations less than 10 μg/mL (e.g., drowsiness, lightheadness) (Evens, Fraser, Ludden, and Sutherland, 1980).

Symptoms associated with rapid intravenous injections of phenytoin include bradycardia, hypotension, and widening of the QRS and QT intervals on an electrocardiogram. These symptoms can be diminished or avoided by injecting the drug slowly not more than 50 mg/min(Evans, Schentag, and Jusko, 1986 ; Schmidt, and Seldon, 1982 ; Salem, Wilder, Yost, Doering, and Lee, 1981).

5. Drug Interaction

Phenytoin is a potent inducer of carbamazepine metabolism, resulting in as much as a 50% reduction in carbamazepine serum concentrations. Phenytoin also induces primidone metabolism, and causes an increase in the primidone-derived phenobarbital/primidone serum concentration ratio from 1.5 to 2.5 to a ratio of approximately 4. Phenytoin may also increase the clearance of acetaminophen, oral contraceptives, steroids, doxycycline, nortriptyline, quinidine, vitamin D, folic acid, pyridoxine, theophylline and dicumarol. Phenytoin has been demonstrated to reduce the renal sensitivity to furosemide and has been found to result in a lower levodopa effect (Taylor and Diescaviness, 1986 ; Faingold and Fromm, 1992 ; Chapron, LaPierre, and Elkair, 1993 ; Inoue and Kolabinski, 1986).

6. Dosage

Oral phenytoin therapy can be initiated at the full maintenance dose, and generally ranges from 5 to 7 mg/kg/d for both adults and children.

Adults: The average maintenance dose rate of phenytoin in adults ranges from 5 to 7 mg/kg/d.

Neonates and Infants(<3 months): Maintenance dose rates as low 3 mg/kg/d may be required within the first few weeks of life because hepatic enzyme activity may be low soon after birth. Gradual increases in this daily dose up to 5 mg/kg/d should be guided by clinical response in conjunction with information from serum phenytoin concentrations. In neonates and infants, loading doses of 15 to 20 mg/kg may also be necessary because of a larger volume of distribution of this group.

Children: The loading dose in children of this age group is 10 to 15 mg/kg; the maintenance dose rate ranges from 5 to 15 mg/kg/d. The body clearance of phenytoin is higher

in infants and children younger than 5 to 6 years old, who require larger daily doses per kilogram of body weight than adults to attain therapeutic serum concentrations.

7. Therapeutic Monitoring of Phenytoin

7.1 Therapeutic and Toxic Serum Concentrations

Phenytoin serum concentrations of 10 to 20 μg/mL are generally accepted as therapeutic. Serum concentrations in range of 5 to 10 μg/mL can be therapeutic for some patients, but concentrations below 5 μg/mL are not likely to be effective. However, Hayes and Kootsikas (1993) reported that many individuals with seizure disorders have full therapeutic response to phenytoin at serum phenytoin concentrations below 10 μg/mL, response at a lower concentration is most likely in individuals with infrequent, primary tonic-clonic seizures.

A number of phenytoin side effects, such as gingival hyperplasia, folate deficiency and peripheral neuropathy, do not appear to be related to serum phenytoin concentrations. In contrast, central nervous system (CNS) side effects do correlate with serum concentration. Nystagmus is probably the most common CNS side effect and usually occurs in patients with serum phenytoin concentrations greater than 20 μg/mL. However, the concentration range associated with the side effect is broad, with some patients showing symptoms at the concentrations of 15 μg/mL and others having no nystagmus with concentrations greater than 30 μg/mL. Other CNS symptoms such as ataxia and dimnished mental capacity are frequently observed in patients with concentrations exceeding 30 and 40 μg/mL respectively (Winter, Katcher and Kimble, 1980 ; Lund, 1974).

7.2 Blood Sampling Times for Phenytoin Serum Assay

The most reliable value to be used for phenytoin dosage adjustments is the trough concentration, obtained at the end of a steady-state dosing interval.

7.3 Specimen Storage

Blood and saliva should be collected with sterile technique. The blood and saliva sample should be centrifuged promptly and the serum or supernatant separeated. Sample not analyzed immediately should be stored frozen at -20°C (Cai, Zhu, Chen, 1993).

7.4 Assay Methods

Three analytical techniques are currently available for measurement of phenytoin serum concentrations. These include spectrophotometry, immunoassay, and chromatography. Chromatographic methods are specific and sensitive enough to measure all the currently used drugs and their metabolites over the full concentration range of clinical interset. These techniques include gas-liquid chromatography, thin-layer chromatography , and high pressure liquid chromatography. Immunoassay techniques have the advantage of being rapid and sensitive. The immunochemical techniques most commonly used are homogeneous enzyme immunoassay and radioimmunoassay. These include the enzyme multiplied immunoassay (EMIT R,Syva, Palo Alto, CA) and fluorescence polarization immunoassay techique (Abbott Laboratories, North Chicago, IL) (Taylor and Diescaviness, 1986; Wilson, Tsanaclis,Williams, Tedstone, and Richens, 1989).

Fluorescence Polarization Immunoassay (FPIA) and TDX^{R}

(Abbott, TDX Training; Jolly, Stroupe, Schwenzer et al., 1981)

The Abbott TDX^{R} system is based on FPIA technique. This method combines competitive protein binding with fluorescence polarization to give a direct measurement without the need for a separation procedure. All competitive binding immunoassays for measuring therapeutic drugs are based on competition between the drug in the patient sample and a labeled drug, called tracer. Sample drug and tracer compete for a limited number of binding sites on antibodies specific to the drug being measured. The concentration of unlabeled drug

from a patient sample will determine how much labeled drug can bind to the spaecific antibody. In the TDX^{R} system , the label on the tracer drug is the fluorescent dye-fluorescein. The changes of polarization angle reflect tracer binding to antibody. The precise relationship between polarization and concentration of the unlabeled drug is established by measuring the polarization valves of calibrators with known concentrations of the drug. A calibration curve stored in system memory is used to automatically determine the concentrations of unknown patient samples.