Can A Massive Phenytoin Toxicity Be Asymptomatic?:

A Case Report

Waleed A.Rahman Abu Lebdeh, Dr.V.P.Gupta, and Dr. M.M.Kabiraj

Riyadh Medical Complex, Central Laboratories, P.O. Box 9120, Riyadh-11413, Saudi Arabia

ABSTRACT

The patient in this case study is a 26-year-old Saudi female with uncontrolled epilepsy. She experienced normal development until her 5th year when she developed epilepsy. From that age she was treated with Tegretol 200 mg two times daily and Phenytoin 100 mg two times daily. When the attending physician suspected drug toxicity, he sent for a drug screening. The screening was performed using ToxiLab, Irvin, USA. Only Phenytoin was present in the screening and this might show the patient was non-compliant to Tegretol medication. If Tegretol was present this would indicate that the Phenytoin levels were more than the measured level, because Tegretol presence might decrease Phenytoin levels by increasing its elimination.

The patient's chest, abdomen, and cardiovascular system were normal. She was admitted after a seizure witnessed by her family. The seizure lasted for 5 minutes and was accompanied by inability to walk. On examination, she was alert and conscious but CT Brain showed atrophy. There was no hepatosplenomegaly and no other stigmata of chronic liver disease. Her Phenytoin level on admission was measured on TDX-FLX Automated Machine and was found to be 92.13 ug/mL. The patient was asymptomatic. Liver function tests indicated the following: Total Protein 75 g/L Albumin 45 g/L Bilirubin 5.2 emol/l Alkaline Phosphatase 86 U/L Alanine Transaminase 16 U/L Aspartate Transaminase 16 U/L. Glucose, Urea and Electrolytes were normal. Phenytoin was stopped and Valium was given when needed by IV. A stomach wash and repeated doses of activated charcoal were administered, and the patient was observed in the ward. Treatment is nonspecific since there is no known antidote.

(Key Words: overdose, toxicity, therapeutic range, lethal dose)

INTRODUCTION

Phenytoin is one of the most widely prescribed anticonvulsants and is occasionally used as a myocardial antiarrhythmic. It blocks voltage-sensitive sodium channels in neurons. This action leads to a delay in neuronal electrical recovery. It prevents the electrical spread of a focus of irritable tissue from entering normal tissue. Most patients will receive maximum seizure control when serum levels of Phenytoin are in the range of 10-20 ug/mL.

Absorption of Phenytoin after oral ingestion is slow, sometimes variable, and occasionally incomplete. Peak concentration in plasma may occur as early as 3 hours after a single dose or as late as 12 hours. After absorption, it is rapidly distributed into all tissues (Godman and

Gilman, 1996). It has a volume of distribution of 0.6 L/kg and is extensively bound to plasma proteins (90%). Blood levels of Phenytoin reflect only total serum concentration of the drug. Only the free unbound Phenytoin has biological activity. Hepatic microsomal enzymes primarily metabolize Phenytoin into an inactive metabolite, which is excreted mainly in the bile, reabsorbed from the intestinal tract, and ultimately excreted in the urine. Less than 5% of Phenytoin is excreted unchanged in the urine. Individuals with impaired metabolic or excretory pathways may exhibit early signs of toxicity. Its metabolism is dose dependent.

DISCUSSION

Elimination follows first-order kinetics (fixed percentage of drug metabolized during a per unit time) at the low drug concentrations and zero-order kinetics (fixed amount of drug metabolized per unit time) at higher drug concentrations (Miller, 2001). This change in kinetics reflects the saturation of metabolic pathways. Thus, very small increments in dosage may result in adverse effect. Since Phenytoin has a narrow therapeutic range, its serum levels should be monitored. Its administration has been associated with toxic effects. Its toxicity depends on the route of administration, duration, exposure, and dosage. The route of administration is the most important determinant of toxicity. It may be administered orally or intravenously (Miller, 2001).

Blood levels of Phenytoin reflect only total serum concentration of the drug. Its toxicity is an uncommon problem seen in clinical practice but hypoalbuminemia, chronic renal failure, hepatic dysfunction and drugs, which interfere with Phenytoin metabolism, are the predisposing factors for toxicity. Common manifestations of toxicity, like confusion and ataxia, are well known. The initial symptoms are nystagmus, ataxia, and dysarthria. Other signs are tremor, hyperflexia, lethargy, slurred speech, nausea, and vomiting. The patient may become comatose and hypotensive. Death is contributed to by respiratory and circulatory depression. The frequency and severity of dose-dependent toxic effects increases as the serum level rises above 20 ug/mL Nystagmus usually appears at 20 ug/ml, ataxia at 30 ug/ml, dysarthria and lethargy appear when the plasma concentrations over 40 ug/ml, but at 50 - 70 ug/mL level fatalities were recorded (Subik & Robinson, 1982).

However, our patient had measured serum Phenytoin level of 92.13 ug/ml, but she was alert, conscious, and asymptomatic. This means that some patients can tolerate a massive dose of phenytoin without resulting in deleterious effect. This could be contributed to inter-individual variation of tolerence. There are marked variations among individuals with respect to phenytoin plasma levels where toxicity may occur (Mosby Inc., 1997). The mean lethal dose in adults is estimated to be between 2-5 grams.

CONCLUSIONS

Our patient could tolerate a massive dose of Phenytoin without any deleterious effect. However, treatment requires withdrawal of the drug, the serum levels should be monitored before restating Phenytoin therapy. The clinician must be aware of the predisposing factors for Phenytoin toxicity such as hypoalbuminemia, chronic renal failure, hepatic dysfunction

and drugs, which inhibit Phenytoin metabolism. We recommend checking serum levels of Phenytoin in epileptics especially those with uncontrolled epilepsy.

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About the Authors:

Waleed A. Rahman Abu Lebdeh, is a specialist in medical technology at Riyadh Medical complex. He has over 15 years of professional experience in the field. Currently, he is pursuing his Ph.D. in Medical Technology from Greenwich University.

Vijay Prakesh Gupta, D.F.M., Ph.D., presently works for the Ministry of Health in Riyadh, Kingdom of Saudi Arabia as Legal Specialist and Clinical Toxicologist. Dr. Gupta also serves as an Adjunct Professor at Greenwich University. He earned his M.B.B.S. from Agra University in India, his D.F.M. in Forensic Medicine from Bangalore University, India and his Ph.D. in Forensic Medicine and Toxicology from Greenwich University. Dr. Gupta is a member of ten international medical, forensic and toxicological societies; has written more than 17 published papers on forensic science and toxicology and received awards for his work in both India and the Kingdom of Saudi Arabia.

Mohammad Kabiraj, M.D., is a Consultant/Neurophysiologist at the Armed Forces Hospital in Riyadh. Dr. Kabiraj earned his MBBS (1969) and his Masters degree (1974) with honors, from Dhaka University, Bangladesh in the field of Physiology. Dr. Kabiraj has conducted physiology studies as a research scholar in Sweden and as an Assistant Professor of Physiology at the King Saud University in Riyadh. His primary research interests lie in the areas of electrodiagnostic medicine and intra-operative monitoring for epilepsy surgery.

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