TOXICITY OF THE ANTIEPILEPTIC DRUG PHENYTOIN AND EFFECT OF HIGH DOSES OF FOLIC ACID AND VITAMIN E ON PHENYTOIN SERUM CONCENTRATION IN EPILEPTIC PATIENTS

THESIS

SUBMITTED FOR PARTIAL FULFILMENT OF MASTER DEGREE IN FORENSIC MEDICINE AND CLINICAL TOXICOLOGY

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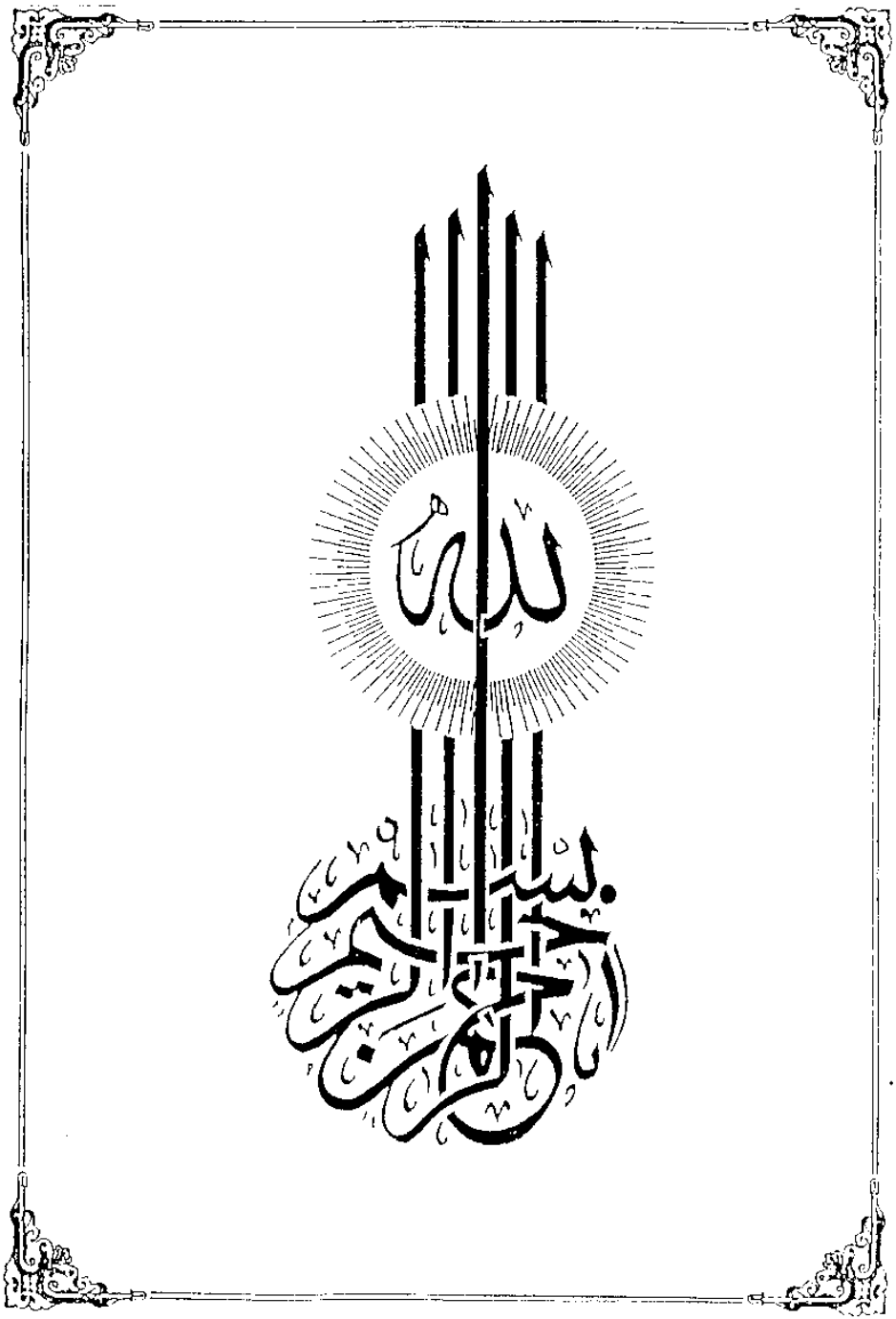
ACKNOWLEDGMENT

I would like to express my sincere gratitude to PROF. DR. SHAWKIA MEHANY ABD-EL GAWAD Professor of Forensic medicine and clinical toxicology Ain Shams University for her continuous supervision, valuable advise, guidance and encouragement.

I would like also to express my deepest thanks and gratitude to PROF. DR. HANY ABD-EL HAKAM GAMAL-EL DIN. Professor of Forensic medicine and clinical toxicology Ain Shams University for his kind supervision, guidance and help throughout this work.

I wish also to express my thankfulness and deepest gratitude to DR. SAMIA ASHOUR MOHAMED HELAL. Lecturer of Neurology and psychiatry Ain Shams University for her guidance, continuous assistance and patient support throughout this work.



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INTRODUCTION

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The therapeutic or prophylactic use of high doses of water-soluble vitamins has grown enormously. It's claimed that "Mega doses" of some vitamins prevent, ameliorate, or cure some types of: cancer, schizophrenia, mental retardation, common cold, epileptic fits, convulsions and a diverse array of other diseases (Wentzter, 1979, Lesser, 1980, and Alhadeff et al., 1984).

However, the high doses of water-soluble vitamins are not without danger. Indeed, they may have toxic effects (Marcus and Coulston 1991). Or may interact with drugs that are concurrently used by means of several mechanism (Dipalma and Ritchie, 1977, Ivey 1979, Schwartz, 1981, and Stockley 1981).

It has been reported that the administration of some vitamins as nicotinamide, B6 and E potentiated anticonvulsant action of some antiepileptic drugs (Kryzhanovskii and Shandra, 1985).

On the other hand, patients on long term therapy with anticonvulsive drugs, have high prevalence of low serum level of vitamins: B2, E, Folic acid and may show signs of vitamin deficiency. (Cimino et al., 1985, Ogunmekan, 1985

and Krause et al., 1988). Accordingly, there is a common belief for epileptics that they should take vitamins frequently with or without medical advice.

AIM OF THE WORK

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The aim of this work is to review the toxicokinetics of the antiepileptic drug phenytoin as well as evaluation of the effect of high doses of folic acid and vitamin E on serum phenytoin level in epileptic patients. More over, the effect of sudden withdrawal of folic acid and vitamin E on phenytoin serum concentration will be studied to explore any relevant alteration of phenytoin serum level that may help understanding the mechanism of the possible interactions.

REVIEW OF LITERATURE

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Epilepsy is a pathological condition, as old as man himself. In old ages, epilepsy was considered as satanic possession and has been very much considered to be related to magic and superpowers. Epilepsy, from the Greek word, meaning seizure, is a chronic brain disorder characterized by irregularly occurring attacks. However the most acceptable definition of epilepsy was introduced by "Brain" in (1971) as" a paroxysmal and transitory disturbance of the function of the brain which develops suddenly, ceases spontaneously and exhibits a conspicious tendency to recurrence".

The precise mechanisms involved in producing the excessive neuronal discharge of epilepsy remain incompletely understood. There are different mechanisms by which a group of neurons become hyperexcited and prone to excessive discharge.

The first theory: Altered neuronal membrane potentials due to decrease in extra cellular Na+ or Ca++ concentration (Kuhar et al., 1976).

The second theory: Altered synaptic transmission as decrease in Gamma Amino Butyric Acid.

GABA- mediated inhibition in certain pathways (Pierre et al., 1976 and Stephen et al., 1971).

The third theory: Altered activity of inhibitory neuronal pool. (Aurther, 1972).

The fourth theory: Altered generalized neuronal excitability (Aurther, 1972).

The fifth theory: Altered epileptic threshold of the brain. (Southerland et al., 1980).

Classification of Epilepsy

There are many classifications of epilepsy. However, which modified from International League Against Epilepsy (ILAE) in 1969 is widely accepted that classifies epilepsy into.

1- Generalized Seizures: (bilaterally symmetrical seizure without local onset) as:-

- Absence (Petit mal)
- Bilateral myoclonus
- Infantile spasm
- Clonic seizures
- Tonic seizures

- Tonic-clonic seizures (Grand mal)
- Akinetic seizures.

2- PARTIAL SEIZURES: (Seizures beginning locally with:

- Elementary symptomatology: Motor-Sensory-Autonomic
- Complex symptomatology (Temporal lobe epilepsy)
- Partial seizures becoming generalized tonic - clonic seizures.

3) UNCLASSIFIED SEIZURES:

Seizures which can't be classified because of incomplete data:

- Status epilepticus
- Petit mal status
- Temporal lobe status
- Focal motor status (Epilepsia partialis continua).
- Inhibitory epilepsy.

ANTI-EPILEPTIC DRUGS: -

There are different varieties of antiepileptic drugs with different mode of action as:-

1) ENHANCEMENT OF INHIBITION THROUGH:

a) Potentiation of GABAergic inhibition e.g.: Benzodiazepines and barbiturates (Olsen, 1988 and Haefely, 1989).

b) GABA receptor agonists as: Progabide (Rogawski and Porter, 1990).

C) Inhibition of the GABA catabolic enzyme GABA transaminase (GABA-T) e.g. vigabatrin.

D) Blockade of GABA uptake into neurons or glia by nipecotic acid analogue e.g. tiagabine

(Nielsen et al., 1991 and Mengel et al., 1990).

2) DIMINUTION OF EXCITATION: by blockade of synaptic excitation mediated by N-Methyl-D-Aspartate (N-MDA) type glutamate receptors. (Grant et al., 1990; Morrisett et al., 1990 and Liljequist, 1991).

3) MODULATION OF Na^+, K^+, AND Ca^{++} CHANNELS as phenytoin (Willow and Catterall, 1982, and Yaari et al., 1986).