

**SERUM PYRIDOXAL (VITAMIN B-6)
CONCENTRATION IN ASTHMATIC CHILDREN
TREATED WITH THEOPHYLLINE**

A THESIS

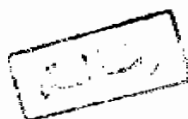
Submitted in Partial Fulfilment for
The Degree of M.Sc. (Pediatrics)

By

Ghada Fikry Abdel Gelil
M.B., B.Ch.

618.9223
G. F.

60966



SUPERVISED BY

Prof. Dr. Karima A. Abd El-Khalek
Professor of Pediatrics, Ain Shams University



Dr. Moustafa M. El-Rasad
Assistant Prof. of Biochemistry, Ain Shams University

Dr. Laila M. Abd El-Ghaffar
Lecturer of Pediatrics, Ain Shams University

[Handwritten signatures and initials]

**Faculty of Medicine
Ain Shams University
1996**



ACKNOWLEDGMENT

I would like to express my sincere and deep gratitude to **PROFESSOR DR. KARIMA A. ABD EL-KHALEK**, Professor of Pediatrics, Faculty of Medicine, Ain Shams University, for her kind supervision, continuous encouragement, and valuable remarks throughout the entire period of this study.

I wish to express my deep appreciation and gratitude to **PROFESSOR DR. MOUSTAFA M. EL-RASAD**, Professor of Biochemistry, Faculty of Medicine, Ain Shams University, for his instructive supervision and valuable directions.

I do feel greatly indebted to **DR. LAILA M. ABD EL-GHAFFAR**, Lecturer of Pediatrics, Faculty of Medicine, Ain Shams University, for sharing her expertise, valuable time, and help for suggestion to ensure the accuracy of this work.

I owe special thanks to my family for their kind help and continuous support.

CONTENTS

	Page
List of Abbreviations	i
List of Tables	iii
List of Figures	v
Chapter I: Introduction and Aim of the Work	1
Chapter II: Review of Literature	3
A. Bronchial Asthma	3
Definition of bronchial asthma	3
Aetiology of asthma	5
Conditions associated with asthma	10
Classification of asthma	12
Physiology of airway receptors	14
Pathology of bronchial asthma	18
Pathophysiology of bronchial asthma	23
Airway hyperresponsiveness	25
Inflammatory cells and asthma	27
Inflammatory mediators involved in bronchial asthma	35
Persistent and latent viral infection in the pathology of asthma	42
Role of nervous system in asthma	45
Asthma variants	49
Diagnosis of bronchial asthma	53
Management strategies of bronchial asthma	60
B. Theophylline	77
Mechanism of action	77
Metabolism	78
Factors affecting metabolism	80

	Page
Drug interactions	81
Theophylline in pregnancy and lactation	83
The effect of theophylline therapy on brain blood flow and function	83
Adverse effect	85
Others possible therapeutic effects	87
C. Vitamin B6	89
Chemistry	89
Absorption-transport-metabolism and excretion	90
Bioavailability of vitamin B6	92
Vitamin B6 sources and requirements	93
Functions of vitamin B6	94
Clinical uses of vitamin B6	100
Vitamin B6 deficiency and dependency	102
Vitamin B6 toxicity	109
Chapter III: Subjects and Methods	111
Chapter IV: Results	119
Chapter V: Discussion	143
Chapter VI: Summary - Conclusion - Recommendations	149
Chapter VII: References	155
Arabic Summary	

LIST OF ABBREVIATIONS

ACTH	Adrenocorticotropin
Adv	Adventia
AEDs	Antiepileptic drugs
AF	Aspergillus fumigatus
AF-IgE	Aspergillus fumigatus-immunoglobulin E
AHR	Airway hyper-responsiveness
ASL	Airway surface liquid
ASM	Airway smooth muscle
BAL	Bronchoalveolar lavage
bm	Basement membrane
C _{3a}	The "a" portion of complement number 3
C _{5a}	The "a" portion of complement number 5
C-AMP	Cyclic adenosine monophosphate
CGRP	Calcitonin gene related peptide
CNS	Central nervous system
COPD	Chronic obstructive pulmonary disease
DSCG	Disodium cromoglycate
DNA	Deoxy nucleic acid
ECF-A	Eosinophil chemotactic factor-A
ECP	Eosinophil cationic protein
EEG	Electroencephalogram
EIA	Exercise induced asthma
Ep-DIF	Epithelium derived inhibitory factor
FEV ₁	Forced expiratory volume in 1st second
FEV ₂	Forced expiratory volume in 2nd second
GABA	Gamma amino butyric acid
GAD	Glutamic acid decarboxylase
GM-CSF	Granulocyte and macrophage colony stimulating factor
3HK	3 hydroxy kynurenine
5HT	5 hydroxy tryptamine
H ₁	Type I histamine receptor
H ₂	Type II histamine receptor
H ₃	Type III histamine receptor
ICU	Intensive care unit
IgE	Immunoglobulin E

IL	Interleukin
M ₁	Type I muscarinic receptor
M ₂	Type II muscarinic receptor
M ₃	Type III muscarinic receptor
MBP	Major basic protein
mRNA	Messenger ribonucleic acid
MPn	Mycoplasma pneumonia
NANC	Non-adrenergic non-cholinergic
NEP	Neutral endopeptidase
NKA	Neurokinin A
NO	Nitric oxide
4PA	4-pyridoxic acid
PAF	Platelet activating factor
PGE ₁	Prostaglandin E ₁
PGE ₂	Prostaglandin E ₂
PL	Pyridoxal
PLP	Pyridoxal-5'-phosphate
PM	Pyridoxamine
PMP	Pyridoxamine phosphate
PN	Pyridoxine
REM	Rapid eye movement
RIA	Radioimmunoassay
RSV	Respiratory syncytial virus
RSV-IgE	Respiratory syncytial virus-immunoglobulin E
SP	Substance P
TGF- β	Transforming factor- β
TH-2	T-helper-lymphocyte-type-2
THR	Thyrotropin-releasing hormone
TLC	T-lymphocyte clone
TNF- α	Tumour necrosis factor- α
V _{max} FRC	Maximal expiratory flow at functional residual capacity
VIP	Vasoactive intestinal peptide
XA	Xanthurenic acid

LIST OF TABLES

	Page
<i>Review of Literature</i>	
Table (1): Autonomic receptors in the airways.	17
Table (2): Mediator receptor in the airways.	17
Table (3): Conditions association with airway hyperresponsiveness.	25
Table (4): Functional changes occurring in asthma.	26
Table (5): Inflammatory mediators released by airway epithelial cells.	39
Table (6): Mechanisms of virus-induced asthma.	44
Table (7): Differential diagnosis of asthma.	55
Table (8): Environmental control.	61
Table (9): Management of chronic asthma in children	62
Table (10): Scheme for oral theophylline dosing.	68
Table (11): Comparative side effect profile of drugs used in treatment of air flow limitation.	71
Table (12): Factors that affect theophylline clearance.	84
Table (13): Side effects of treatment with high dose of vitamin B6 (Pyridoxine HCl).	101
Table (14): Development of Vitamin B6 deficiency.	105
Table (15): Immune function changes in B-group vitamin deficiency states	108
<i>Results</i>	
Table (1): Plasma pyridoxal -5'-phosphate (PLP) concentration in control and cases before theophylline treatment.	121
Table (2): Plasma pyridoxal-5'-phosphate concentration in control, mild and moderate cases before theophylline treatment.	123
Table (3): Plasma pyridoxal-5'-phosphate concentration in mild and moderate asthmatic cases before theophylline treatment.	124
Table (4): Plasma pyridoxal-5'-phosphate (PLP) concentration in control, mild and moderate cases after theophylline treatment.	126
Table (5): Plasma pyridoxal-5'-phosphate (PLP) concentration in mild and moderate cases after theophylline treatment.	127

	Page
Table (6): Plasma pyridoxal-5'-phosphate (PLP) concentration in all cases before and after theophylline treatment.	129
Table (7): Plasma pyridoxal-5'-phosphate concentration in mild cases before and after theophylline treatment.	131
Table (8): Plasma pyridoxal-5'-phosphate (PLP) concentration in moderate group before and after theophylline treatment.	133
Table (9): Plasma pyridoxal-5'-phosphate (PLP) concentration in males and females.	135
Table (10): Correlation between age and plasma pyridoxal -5'-phosphate (PLP) concentration.	135
Table (11): Clinical and laboratory data of cases.	140
Table (12): Clinical and laboratory data of control.	141

LIST OF FIGURES

	Page
<i>Review of Literature</i>	
Fig. (1): Factors which contribute to the development of asthma symptoms.	8
Fig. (2): Schematic diagram of the wall of an intraparenchymal airway.	19
Fig. (3): Schematic diagram of an airway wall before and after smooth muscle contraction.	22
Fig. (4): Pathophysiology of bronchial asthma	24
Fig. (5): Relationship between airway inflammatory changes in asthma and the clinical component of the disease	28
Fig. (6): Mast cell secretagogues.	30
Fig. (7): Cellular interactions leading to eosinophil infiltration and epithelial injury	34
Fig. (8): Nocturnal asthma: Potential mechanisms	49
Fig. (9): Diagnosis of asthma in children unable to perform lung function tests.	56
Fig. (10): Diagnosis of asthma in children able to perform lung function tests	57
Fig. (11): Management of asthma in the first year of life	72
Fig. (12): Management of asthma in the 1-3 year age group	73
Fig. (13): Management of asthma in the 3-5 years age group.	74
Fig. (14): Management of asthma in the 5-18 years age group	75
Fig. (15): Management of acute severe asthma.	76
Fig. (16): Biotransformation of theophylline in human.	79
Fig. (17): Free and phosphorelated forms of vitamin B6.	89
Fig. (18): The proposed relationship between plasma pyridoxal-5'-phosphate (PLP), pyridoxal (PL), pyridoxine (PN) and extra hepatic vitamin B6 metabolism.	92
Fig. (19): Pyridoxine-5'- B-D-glucoside.	93
Fig. (20): Involvement of vitamin B6 in the central nervous system.	96
Fig. (21): Participation of vitamin B6 in GABA metabolism.	97
Fig. (22): Vitamin B6 and glucocorticoid receptors.	99
Fig. (23) Structural formula of thiazolidine, the product of penicillamine-pyridoxine reaction.	104
Fig. (24): Typical standard curve of pyridoxal-5'-phosphate (PLP) concentration.	118

Results	Page
Fig. (1): Distribution of the studied subjects.	119
Fig. (2): Mean age of control, cases, mild and moderate groups.	120
Fig. (3): Mean PLP level in males and females in control and cases before theophylline treatment.	122
Fig. (4): Mean PLP levels in control cases, mild and moderate groups before treatment.	125
Fig. (5): Mean PLP levels in control, cases, mild and moderate groups after treatment.	128
Fig. (6): Mean PLP levels in all cases before and after treatment.	130
Fig. (7): Mean PLP levels in mild group before and after treatment.	132
Fig. (8): Mean PLP levels in moderate group before and after treatment.	134
Fig. (9): Correlation between age and PLP level in controls.	136
Fig. (10): Correlation between age and PLP levels in the cases.	137
Fig. (11): Mean PLP level in control, cases, mild and moderate groups before and after theophylline therapy.	139

CHAPTER I

Introduction and Aim of The Work

