

Acetylcholine and Posttraumatic Stress Disorder

Elizabeth A. Goble

Thesis submitted for the degree of

Master of Science

in

Psychiatry

at

The University of Adelaide

Discipline of Psychiatry

School of Medicine

April 7, 2009

Contents

List of Tables	ix
List of Figures	xi
Signed Statement	xiii
Acknowledgements	xv
Dedication	xvii
Abstract	xix
List of Abbreviations	xxi
1 Introduction	1
1.1 Acetylcholine	2
1.1.1 The Acetylcholine Pathway	2
1.1.2 Acetylcholine Receptors	3
1.1.3 The Cholinergic System	4
1.1.4 Functional Correlates of Acetylcholine	7
1.1.4.1 Learning and Memory	9
1.1.4.2 Attention	11
1.1.4.3 Cognition	12
1.1.5 Neurotransmitter Interactions Involving the Cholinergic System	12

1.1.5.1	Serotonin	13
1.1.5.2	Catecholamines	14
1.1.5.3	GABA	15
1.1.5.4	Glutamate	15
1.1.6	Conditions with Altered Cerebral Cholinergic Function	15
1.1.6.1	Alzheimer's Disease	16
1.1.6.2	Lewy Body Dementia	17
1.1.6.3	Schizophrenia	17
1.1.6.4	Parkinson's Disease	18
1.1.6.5	Excesses of ACh	19
1.1.7	Therapeutic Enhancement of Central Cholinergic Function	20
1.1.7.1	Acetylcholinesterase Inhibitors	21
1.2	Posttraumatic Stress Disorder	23
1.2.1	Historical Aspects	23
1.2.2	Epidemiology	24
1.2.3	Definition and Diagnosis	24
1.2.3.1	Psychological Assessments	26
1.2.4	Currently Available Treatment Modalities	27
1.2.5	The Pathogenesis of PTSD	27
1.2.5.1	Anatomical	28
1.2.5.2	Neurochemical	29
1.2.6	Functional Changes in PTSD	30
1.2.6.1	Learning and Memory	30
1.2.6.2	Cognition	31
1.2.6.3	Attention	32
1.2.6.4	Mood/Behavioural Issues and Secondary Effects	32
1.2.7	The Cholinergic Neurotransmitter System in PTSD	33
1.2.7.1	ACh and Stress	33
1.2.7.2	Previous PTSD Studies - ACh and PTSD	34

1.2.7.3	Basis for Considering a Potential Role for ACh Neurotransmission	34
1.2.8	Cerebral Imaging and Other Activity Investigations of PTSD	36
1.2.9	Scope of the Present Study	38
2	The I¹²³ Iododexetimide (IDEX) SPECT Study	41
2.1	INTRODUCTION	41
2.1.1	Aim	44
2.2	METHOD	44
2.2.1	Recruitment	44
2.2.1.1	Inclusion Criteria	46
2.2.1.2	Exclusion Criteria	46
2.2.1.3	Funding and Approval	46
2.2.2	Procedure	48
2.2.2.1	Patient Preparation and Administration	48
2.2.2.2	Psychological Assessments	50
2.2.2.3	IDEX SPECT Image Acquisition and Processing	53
2.2.2.4	MRI Acquisition and Processing	54
2.2.3	SPECT Data Analysis	54
2.2.3.1	SPM Pre-processing	55
2.2.3.2	Global Scaling	55
2.2.3.3	SPM Statistics	57
2.2.3.4	SnPM Statistics (non-parametric)	59
2.3	RESULTS	60
2.3.1	Demographic Characteristics	60
2.3.2	Psychological Assessment Results	61
2.3.3	Procedural Results	63
2.3.4	SPM Statistical Results	66
2.4	DISCUSSION	71

2.4.1	Regions of Interest and Clinical Relevance of Alterations in ACh . . .	71
2.4.1.1	Precuneus	71
2.4.1.2	Insula	73
2.4.1.3	Parahippocampus	74
2.4.1.4	Caudate	75
2.4.1.5	Combination or Network Effects	76
2.4.2	Study Limitations	77
2.5	CONCLUSION	78
3	The Donepezil Clinical Trial	81
3.1	INTRODUCTION	81
3.1.1	Donepezil	82
3.1.2	Aim	85
3.2	METHOD	86
3.2.1	Study Design	86
3.2.2	Recruitment	87
3.2.2.1	Inclusion Criteria	87
3.2.2.2	Exclusion Criteria	87
3.2.2.3	Funding and Approval	87
3.2.3	Procedure	88
3.2.3.1	Study Medication	89
3.2.3.2	Psychological Assessments	89
3.2.3.3	Statistical Analysis	91
3.3	RESULTS	92
3.3.1	Demographic Characteristics	92
3.3.2	Psychological Assessment Results	94
3.3.2.1	Per-protocol Analysis	94
3.3.2.2	Intention-to-treat Analysis	102
3.3.2.3	Subjects Who Withdrew	103

3.3.3	Anecdotal Accounts	106
3.4	DISCUSSION	107
3.4.1	Study Limitations	110
3.5	CONCLUSION	111
4	Summary	113
4.1	Posttraumatic Stress Disorder and Acetylcholine	113
4.2	The IDEX Study	115
4.3	The Donepezil Study	117
4.4	Future Directions	119
	Appendices	121
A	Pharmacy Information: Medications with Cholinergic Properties	121
B	IDEX Study Ethics Approval Letter	123
C	IDEX Study Patient Information and Informed Consent Form	125
D	Issues Influencing IDEX Supply	127
E	Optimisation Paper	129
F	Donepezil Study Ethics Approval Letter	131
G	Donepezil Study Patient Information and Informed Consent Form	133
H	Donepezil Approved Product Information	135
	Bibliography	136

List of Tables

1.1.1	Classification of Cholinergic Neurons	5
1.1.2	Memory Terms, Definitions and Tests	10
2.3.1	The IDEX Psychological Scale Results Acquired for All Subjects	62
2.3.2	The Summary of Results Obtained for the SPM Analysis	65
2.3.3	The Results for SPM Analysis for Differences in ACh Activity	66
3.2.1	The Schedule of Visits and Assessments	86
3.3.1	Summary of Side Effects	93
3.3.2	The Psychological Score Differences Over Time	95
3.3.3	The PTSD Check List (PCL) Results	96
3.3.4	The Clinician-Administered PTSD Scale (CAPS) Results	97
3.3.5	The Treatment Outcome PTSD Scale (TOP8) Results	98
3.3.6	The Impact of Events Scale (IES) Results	99
3.3.7	The Beck Depression Index (BDI) Results	100
3.3.8	The Hamilton Depression Scale (HAMD) Results	101
3.3.9	The Psychological Score Differences Over Time	102
3.3.10	The Intention-to-treat Statistics Summary	103
3.3.11	Completers Versus Subjects who Withdrew	104
3.3.12	The Psychological Score Differences Over Time for the Subjects who Withdrew	105

List of Figures

1.1.1	The Acetylcholine Pathway	2
1.1.2	Summary of Cholinergic Projections	6
1.1.3	The Basal Forebrain Cholinergic System Functions	8
2.2.1	Recruitment Flow Chart	47
2.2.2	IDEX Procedure Timeline	49
2.2.3	IDEX SPM Pre-processing Flow Chart	56
2.2.4	Template For Scaling to the Basal Ganglia	57
2.2.5	SPM Statistical Print Out	58
2.3.1	Slices of MRI Showing IDEX Uptake Deficits	67
2.3.2	Cluster Volume Summary	68
2.3.3	SPM and MRI Overlay of <i>Reduced</i> ACh Receptor Activity	69
2.3.4	SPM and MRI Overlay of <i>Increased</i> ACh Receptor Activity	70
3.1.1	The Structure of Donepezil	83

Signed Statement

This work contains no material which has been accepted for the award of any other degree or diploma in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text.

I consent to this copy of my thesis, when deposited in the University Library, being available for loan and photocopying.

SIGNED: DATE:

Acknowledgements

I would like to sincerely thank all those who assisted me in completing this work, and acknowledge each for their individual contributions, as follows:

Dr. M. Anne Hamilton-Bruce (Medical Scientist/Supervisor) for providing scientific advice, assistance with data analysis and interpretation, thesis preparation and critical review.

Dr. Leighton R. Barnden (Nuclear Physicist/Nuclear Medicine Supervisor) for providing radiological experience and advice, assistance with study design, data collection, data analysis and interpretation, thesis preparation, and critical review of the Nuclear Medicine component of the research.

Prof. A.C. McFarlane (Psychiatrist/Principal Supervisor 2001-2004) and Assoc. Prof. Richard Clark (Psychologist, Flinders University/Supervisor 2001-2004) for PTSD experience and clinical advice, and assistance with study design of the Donepezil Clinical Trial.

Dr. Geoff Schrader (Psychiatrist/Principal Supervisor 2005-2008) for critical review during thesis preparation and for taking up supervision of the project after Prof. McFarlane left The Queen Elizabeth Hospital Psychiatry Department.

Dr. Nick Potts (Psychiatrist) for clinical advice, performing all psychiatric monitoring of subjects and providing patient care and follow up where necessary during the course of the Donepezil Clinical Trial.

Dr. Rey Casse (Nuclear Medicine Physician/Neurologist) for specialist information regarding the Neuroanatomical aspects of the IDEX trial.

Dr Bill Burch (Nuclear Physicist, ANSTO) for support and expertise in liaising with ANSTO to provide the IDEX.

Technologists in TQEH Nuclear Medicine Department for patient handling and acquiring the IDEX images.

Dr. Daniel Badger (Nuclear Medicine Physicist) for assistance with the LaTeX software used in the generation of this thesis.

Nancy E. Briggs (Statistician, Data Management and Analysis Centre, University of Adelaide) for completing the Intention-to-treat statistical analysis of the Donepezil Clinical Trial data.

My extended family and friends for support during the long and challenging years.

Dedication

To my four daughters,
Charlotte (RIP), Emily, Maddison and Sarah,
who were all born during the conduct of this research.

Abstract

Posttraumatic Stress Disorder (PTSD) is a psychiatric condition that can develop following exposure to a traumatic event involving actual or threatened death or serious injury. Responses include intense fear, helplessness or horror. Symptoms are characterised into clusters, described as re-experiencing, avoidance, and arousal. These symptoms, which are also evident in other conditions, have been associated with dysfunctions in the central acetylcholinergic system. Benefits from administering acetylcholinesterase inhibitors (AChEI) to people suffering these symptoms have been demonstrated. Donepezil hydrochloride, a reversible inhibitor of the enzyme acetylcholinesterase, is used in the treatment of conditions with difficulties in cognitive function, but has not been used in PTSD.

The aim of this thesis was to determine (1) whether there was a difference in the ACh system in people with PTSD and (2) whether administration of an AChEI would change the symptomatology.

IDEX (I^{123} iododexetimide) has been useful in imaging muscarinic-ACh receptors using Single Photon Emission Computerised Tomography (SPECT) and was utilised to investigate whether cholinergic activity in PTSD is altered. One hundred and sixty eight potential subjects were screened and eleven PTSD subjects were enrolled in the IDEX SPECT study. Three healthy non-PTSD control subjects also completed the study. Due to technical complications only the data obtained from eight PTSD and two control subjects was available for analysis. Imaging data for 2 further healthy non-PTSD control subjects were obtained from another study. Sixteen subjects were enrolled in the donepezil open label study (assessed at baseline, Week 2, 6 and 10). Nine PTSD subjects completed the 10-week trial and seven withdrew prematurely (at or after Week 2) due to side effects or a worsening of

PTSD symptoms.

For the IDEX SPECT study, a voxel-by-voxel statistical analysis of the PTSD subject group versus the control group showed both areas of reduced and increased IDEX uptake. Significant clusters in the PTSD group with a **reduced** IDEX uptake centred around the bilateral hippocampus, left insula and right precuneus, while **increased** IDEX uptake appeared in the caudate head.

For the donepezil study, in the per-protocol analysis (including only the 9 subjects that completed the protocol), all psychological assessments revealed a difference between the totals obtained at the Week 10 visit compared to those at the Baseline visit and the improvement was in the order of 51%. The intention-to-treat analysis (including all 16 subjects), a repeated measures Analysis of Variance (ANOVA) with a mixed models approach showed that all psychological measures demonstrated statistically significant benefits of the treatment. All subjects who completed the protocol recounted considerable improvement in their overall PTSD symptom profile, which covered symptoms in each of the three clusters.

The results of the IDEX SPECT study suggest that alterations in ACh binding in PTSD are evident and may begin to explain a part of the altered cognitive symptomatology apparent in this condition. The pilot open label donepezil trial provided some preliminary evidence that treatment with an AChEI can lessen the intrusions and distress associated with traumatic memories in people with PTSD.

List of Abbreviations

5-HT	Serotonin
^{99m}Tc -HMPAO	99m -technetium-hexamethylpropyleneamineoxime
ACh	Acetylcholine
AChE	Acetylcholinesterase
AChEI	Acetylcholinesterase Inhibitor
AChE-E	Acetylcholinesterase - Erythrocytic
AChE-R	Acetylcholinesterase - Readthrough
AChE-S	Acetylcholinesterase - Synaptic
AD	Alzheimers Disease
ADAS-Cog	The Alzheimers Disease Assessment Scale - Cognitive Subscale
AINSE	Australian Institute of Nuclear Science and Engineering
ANOVA	Analysis of Variance
ANSTO	Australian Nuclear Science and Technology Organisation
CAPS	Clinician-Administered PTSD Scale for DSM-IV
CBT	Cognitive Behavioural Therapy
ChAT	Choline Acetyltransferase
CIDI	Composite International Diagnostic Interview
CNS	Central Nervous System
CTN	Clinical Trial Notification

dbB	Diagonal Band of Broca
DLB	Lewy Body Dementia
DSM-III-R	Diagnostic and Statistical Manual of Mental Disorders - Third Edition revised
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders - Fourth Edition
E2020	Donepezil - an AChEI
EMDR	Eye Movement Desensitisation and Reprogramming
ENA-713	Rivastigmine - an AChEI
ERP	Event Related Potential
FBE	Full Blood Examination
FDG	Fluorodeoxyglucose
fMRI	Functional Magnetic Resonance Imaging
FWHM	Full Width, Half Maximum
GABA	Gamma-Aminobutyric Acid
GHQ	General Health Questionnaire
HDB	Horizontal Limb of the Diagonal Band of Broca
HPA-axis	Hypothalamic - Pituitary - Adrenocortical Axis
ICD-10	International Classification of Diseases
IDEX	I ¹²³ Iododexetemide
IES	The Impact of Events Scale
IQ	Intelligence Quotient
K+	Potassium ions
LC	Locus Ceruleus
m-AChR	Muscarinic ACh Receptors
MBq	mega-Becquerel
MG	Myasthenia Gravis
MMSE	Mini-Mental State Examination

MRI	Magnetic Resonance Imaging
mRNA	Messenger Ribonucleic Acid
MS	Medial Septal Nucleus
Na+	Sodium ions
n-AChRs	Nicotinic Acetylcholine Receptors
NART	The National Adult Reading Test - Second Edition
nbm	Nucleus Basalis of Meynert
NE	Noradrenaline
NWAHS	North West Adelaide Health Service
PCL-C	Posttraumatic Stress Disorder Check List - Civilian
PCL-M	Posttraumatic Stress Disorder Check List - Military
PD	Parkinson's Disease
PET	Positron Emission Tomography
PFC	Prefrontal Cortex
PTSD	Posttraumatic Stress Disorder
rCBF	Regional Cerebral Blood Flow
SD	Standard Deviation
SNRI	Serotonin-Norepinephrine Reuptake Inhibitor
SNS	Sympathetic Nervous System
SPECT	Single Photon Emission Computerised Tomography
SPM	Statistical Parametrical Map
SSRI	Selective Serotonin Reuptake Inhibitor
TGA	Therapeutic Goods Administration
TQEH	The Queen Elizabeth Hospital
VChAT	Vesicular Choline Acetyltransferase
VDB	Vertical Limb of the Diagonal Band of Broca
WHO	World Health Organization