Ongoing Statin Therapy Lowers Risk for Delirium in ICU

Submitted for partial fulfillment for Master Degree in intensive care

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2015

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Abbreviations

Ab	Amyloid b
ACCESS	Atorvastatin Comparative Cholesterol Efficacy and Safety Study
AD	Alzheimer's disease
APACHE II score	Acute Physiology and Chronic Health Evaluation II score
APC	antigen presenting cells
Apo	Apolipoprotein,
APOE	Apoliprotein E
ATP II	Adult Treatment Panel II
ATP III	Adult Treatment Panel III
AUC	Area Under The Curve
Bax/Bcl-2	Bcl-2 associated X protein
BBB	Blood–Brain Barrier
BDNF	Brain-derived neurotrophic factor
CBF	Cerebral Blood Flow
CHD	Congestive Heart Disease
CNS	Central Nervous System
COMT	Catechol-o-methyl transferase
CSF	Cerebrospinal Fluid
CT	Computerized tomography
CYP 2C8	cytochrome P 2C8 enzyme system
CYP 2C9	cytochrome P 2C9 enzyme system
CYP 3A4	cytochrome P 3A4 enzyme system

CYP450	cytochrome P450 family of enzymes
D2	Dopamine 2 receptor
DRD3	Dopamine receptor D3
eNOS	endothelial Nitric Oxide Synthase
ERK	Extracellular-Signal Regulated Kinase
FPP	farnesyl pyrophosphate
GABA	Gamma-aminobutyric acid
GGPP	geranylgeranyl pyrophosphate
GSK-3b	glycogen synthetase kinase 3b
HDL-C	high density lipoprotein cholesterol
HIV	Human immunodeficiency virus
HMG-CoA	hydroxymethylglutaryl coenzyme A
IC50	The half maximal inhibitory concentration
ICAM-1	intercellular adhesion molecule-1
IDL	intermediate-density lipoproteins
IFN-γ	Gammainterferon
IL-1 b	Interleukin 1 b
IL-6	Interleukin 6
iNOS	inducible or inflammatory nitric oxide synthase
LDL-C	low-density lipoprotein cholesterol
LFA-1	leukocyte function antigen-1
LNAA	large neutral amino acid

Log D	(Distribution co-efficient): used as a measure of lipophilicity.
LOS	length of stay
LPS	Lipopolysaccharide
LTCI	long-term cognitive impairment
MAOA	monoamine oxidase A
MCP	Monocytic chemoattractant protein.
MHC	Major histocompatibility complex
MIP-1α	Macrophage Inflammatory Proteins 1 alpha
MMSE scores	Mini Mental-State Examination scores
MPTP	N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine
MRI	Magnetic resonant imaging
MS	multiple sclerosis
NADPH	Nicotinamide adenine dinucleotide phosphate-enzyme complex
NCEP	National Cholesterol Education Program
NMDA	N-methyl-D-aspartate receptor
nNOS	neuronal nitric oxide synthase
NO	nitric oxide
non-HDL-C	non-high density lipoprotein cholesterol
PAI-1	plasminogen-activator inhibitor 1
PAR-1	protease-activated receptor 1
PD	Parkinson's disease
PKB/Akt	protein kinase B(neuroprotective protein)

POCD	postoperative cognitive dysfunction
PPAR	peroxisome proliferator-activated receptors
ROCK	Rho-associated kinase
SAA	serum anticholinergic activity
SPARCL trial	Stroke Prevention by Aggressive Reduction of Cholesterol Levels trial
TBI	traumatic brain injury
TC	total cholesterol
TG	Triglycerides
Th1	T helper cell 1
Th17	T helper 17 cells
T_{max}	peak plasma concentration
TNF	Tumor necrosis factor
TNF-R1	Tumor necrosis factor receptor 1
TNF-R2	Tumor necrosis factor receptor 2
TNF-α	Tumor necrosis factor alpha
tPA	tissue plasminogen activator
Treg	Regulatory T cells
VCAM-1	vascular cell adhesion molecule-1
VEGF	vascular endothelial growth factor
VEGFR2	vascular endothelial growth factor receptor 2
VLDL	very-low-density lipoprotein
vWF	von Willebrand Factor

Xp11.23 locus	the proximal part of the X-chromosome in location 11.23

INTRODUCTION

❖ Introduction

Delirium is the most common behavioral manifestation of acute brain dysfunction, which occurs in about 60% to 80% of mechanically ventilated patients and 50% to 70% of non-ventilated ICU patients **(Thomason et al., 2005)**. Delirium is defined as an acute change or fluctuation in mental status, inattention, or an altered level of consciousness.**(King&Gratrix,2009)**. During the ICU stay, acute delirium is associated with complications of mechanical ventilation including nosocomial pneumonia, self-extubation, and reintubation. **(Miller et al., 2006)**

A firm understanding of the pathophysiologic mechanisms of delirium remains elusive despite improved diagnosis and potential treatments .Several theories have been proposed to explain the pathophysiology of delirium including neuroanatomic structural changes, sedatives ,analgesics, sepsis, biomarkers ,neurotransmitters, surgical factors , postoperative cognitive dysfunction (POCD), and future directions such as molecular genetics. **(Gunther et al., 2008)**

Statins are not only lipid lowering drugs by inhibiting the hydroxy-methyl-glutaryl-CoA (HMG-CoA) reductase enzyme, the rate limiting enzyme in cholesterol biosynthesis, it's also have diverse effects on the cellular mediators of inflammation that may be partially responsible for their efficacy in preventing neuroinflammatory diseases, statins have potential anti-inflammatory effects which is interpreted (through)

playing a pivotal role in reducing plasma levels of inflammatory markers such as high sensitivity C-reactive protein (hs-CRP) and serum amyloid A. Statins also have direct inhibitory effects on T-cell activation and function, influencing both innate and adaptive immunity, inhibits release of interleukin1(IL-1) and interleukin 6 (IL-6) **(Pasterkamp & Lammeren,2010)**

The anti-inflammatory and immunomodulatory actions of statins reduce delirium by reducing neuroinflammation which is believed to be a significant factor in delirium pathophysiology in critically ill patient. **(Zeiser et al., 2009)**

Aim of the study

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The aim of the study is to understand the role of ongoing use of statins therapy in lowering the risk of delirium in critically ill patient.

Pharmacology of Statins

Pharmacology of Statins

❖ *Introduction*

Statins are the drugs of first choice for management of many lipid disorders. These drugs share many features, but also exhibit differences in pharmacologic attributes that may contribute to differences in clinical utility and effectiveness in modifying lipid risk factors for coronary heart disease. Some of the features desired with statin therapy include potent reversible inhibition of hydroxymethylglutaryl coenzyme A(HMG-CoA) reductase,the ability to produce large reductions in low-density lipoprotein cholesterol (LDL-C) and non-high density lipoprotein cholesterol (non-HDL-C), the ability to increase HDL cholesterol (HDL-C), tissue selectivity (which focuses on treatment effects), optimal pharmacokinetics that limits systemic bioavailability and offers once a day dosing ,and a low potential for drug–drug interactions.**(Mckenney.,2003)**

❖ *Inhibition of Hydroxymethylglutaryl Coenzyme A Reductase*

All statins interfere with the conversion of HMG-CoA to the cholesterol precursor mevalonate by HMG-CoA reductase, an early and rate-limiting step in cholesterol synthesis .Statins competitively inhibit HMG-CoA reductase by binding to the enzyme and sterically inhibiting substrate binding. The degree of inhibition exhibited by statin compounds may differ depending on the strength of their bond to the enzyme. Recent molecular studies have provided insights into the binding