Ongoing Statin Therapy Lowers Risk for Delirium in ICU

Submitted for partial fulfillment for Master Degree in intensive care

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Contents

List of figures	
List of tables	
Abbreviation	
Introduction	1
Aim of the study	3
Pharmacology of statins	4
 Pathophysiology of delirium in ICU 	-24
 Other Lines of management of delirium 	44
❖ Role of statins in lowering risk of delirium in ICU	- - 51
Summary	72
* References	74
* Arabic summary	-1-2

List of figures

FIG (1): chemical structure of Statin-HMG-CoA reductase complexes showing binding characteristics.	6
FIG (2): Inhibition of purified human hydroxymethylglutaryl coenzyme A reductase catalytic domain by statins.	9
FIG (3): Schematic representation of statin mechanism of action.	9
FIG (4): Effects of rosuvastatin and atorvastatin at 52 weeks.	11
FIG (5): Effect of atorvastatin 10 mg and niacin on low-density lipoprotein Cholesterol (LDL-C) subfractions in patients with atherogenic dyslipidemia.	11
FIG (6): (A) Relative lipophilicity/hydrophilicity of statins given as statin octanol-water coefficients.(B) Log ratios of hydroxymethylglutaryl coenzyme A reductase inhibition for hepatocytes: fibroblasts among statins.	13
FIG (7): Conceptual framework for exploring the interrelationship between delirium and dementia.	28
FIG (8): Neurotransmitters and biomarkers of delirium. The evidence supports multiple mechanisms of delirium, which may pertain in different clinical situations.	33
FIG (9): Schematic overview of some mechanisms of statins on lipid metabolism and cellular signaling in neuroprotection.	47
FIG (10): schematic overview of Statin effects in delirium.	52
FIG (11): The systemic inflammatory cascade, effects of delirium, and sites of action for statins in critical illness. pleiotropic effect of statins on the inflammatory cascade	56
FIG (12): The microglia phenotypes, effects of delirium, and hypothesized mechanism of action of statins in critical illness.	60

List of tables

Table (1): Summary: Pharmacological properties of statins.	15
Table (2): Pharmacokinetic properties of statins.	18
Table (3): Partial Listing of CYP3A4 inhibitors and substrates	20
Table (4): Risk factors for delirium in ICU	26

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
СТ	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)		
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	Log D	(Distribution co-efficient): used as a measure of lipophilicity.
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PAI-1 plasminogen-activator inhibitor 1 PAR-1 protease-activated receptor 1 PD Parkinson's disease	NO	nitric oxide
PAR-1 protease-activated receptor 1 PD Parkinson's disease	non-HDL-C	non-high density lipoprotein cholesterol
PD Parkinson's disease	PAI-1	plasminogen-activator inhibitor 1
	PAR-1	protease-activated receptor 1
PKB/Akt protein kinase B(neuroprotective protein)	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
$T_{ m max}$	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
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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



Aim of the study

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