Role of nitric oxide and vasoactive intestinal peptide on gastro-esophageal motility in chronic renal failure patients

Thesis submitted for partial fulfillment of the
M.D. Degree in internal medicine

By

Waleed Anwar Mohamed Abdel Mohsen
M.B.,B.Ch.-M.Sc, Ain Shams University

Supervised by

Prof. Dr. Badawy Labib Mahmoud
Professor of internal Medicine and Nephrology
Faculty of Medicine-Ain Shams University

Prof. Dr. Yehia Mohamed El-Sayed El-Shazly
Professor of internal Medicine and Gastroenterology
Faculty of Medicine-Ain Shams University

Prof.Dr. Hesham Mohamed El-Sayed
Professor of internal Medicine and Nephrology
Faculty of Medicine-Ain Shams University

Prof.Dr. Magdy Mohamed Said El-Sharkawy
Assistant professor of internal Medicine and Nephrology
Faculty of Medicine-Ain Shams University

Faculty of Medicine- Ain Shams University
2008

Acknowledgment

First of all I pray thanking ALLAH, for helping me to go through and to accomplish this work.

I would like to express my deep thanks and extreme graditude to ***Prof. Dr. Badawy Labib Mahmoud***, professor of internal medicine and nephrology, Ain Shams University, for his constant encourgment and help; starting from selection of the subject and continous valuable advice and guidance. My deep indeptedness to him is far shorter than his rights.

Words can not express my profound graditude and sincere appreciation for the help of ***Prof. Dr. Yehia Mohamed El-Sayed El-Shazly***, Professor of internal Medicine and Gastroenterology, the head master of gastrointestinal motility unit, Ain Shams University, that he gave a great deal of his valuable time for this work, and for his sincere unlimited help, support and supervision throught the study.

A special thanks and great appreciation to ***Prof. Dr. Hesham Mohamed El-Sayed***, Professor of internal Medicine and Nephrology, Ain Shams University, for his efforts, his constructive criticism and instructions and for his continous encorgment throught this work.

I am gratefully expressing my sincere appreciation to ***Prof. Dr. Magdy Mohamed Said El-Sharkawy***, Assistant professor of internal Medicine and Nephrology, Ain Shams University, for his kindness, great help, understanding and cooperation, without him, work would never been done.

Finally, I wish to extend my deep thanks to all who had participated in this study for their cooperation especially, Dr. Nanees Ahmed Adel, Dr. Ingy Yosry Elsaid, Dr. Inas Elkhedr Mohamed, Dr. Neveen Ibrahim Mosa, Dr. Mohamed Soliman Eldebiky and Dr. Rasha Elrefaay for their great help and efforts in the practical portion of the study.

CONTENTS

List of Abbreviations

- **5HT:** serotonin
- **Ach:** acetylecholine.
- **ADMA:** asymmetrical dimethyl L-arginine.
- **Alb:** albumin.
- **AP:** Aperistalsis.
- **ATP:** Adenosine-5`-Triphosphate.
- **BER:** basic electrical rhythm.
- **BUN:** Blood urea nitrogen.
- **cAMP:** Cyclic Adenosine Monophosphate.
- **CCK:** Cholecystokinin.
- **Chol:** cholesterol.
- **cNOS:** constitutive nitric oxide synthatase.
- **COMT:** Catechol-O-MethylTransferase.
- **CPM:** cycle per minute.
- **Cr.Cl:** creatinine clearance.
- **Cr:** Creatinine.
- **CRF:** Chronic renal failure.
- **DF:** Dominant Frequency.
- **DOS:** Diffuse esophageal spasm.
- **ECA:** Electrical Control Activity.
- **EGG:** Electrogastrogram.
- **eNOS:** endothelial nitric oxide synthatase.
- **ENS:** enteric nervous system
- **EPSPs:** excitatory postsynaptic potentials.
- **IPSPs:** inhibitory postsynaptic potentials.
- **LES:** lower esophageal sphinter
- **LESP:** lower esophageal sphincter pressure.
- **LNMMA:** NG-monomethyl L-arginine.
- **MCDT:** mixed connective tissue disease.
- **MMC:** migrating motor complex.
- **NADPH:** Reduced Nicotinamide Adenine Dinucleotide Phosphate.
- **NK 1,2:** Neurokinin receptors 1, 2.
- **NANC:** non adrenergic non cholinergic
- **nNOS:** neuronal nitric oxide synthatase
- **NO:** nitric oxide.
- **NO2/NO3:** Nitrate/Nitrite.
- **NOS:** nitric oxide synthatase
- **NSMD**: Non Specific Motility Disorder.
- **NUD**: non ulcer dyspepsia
- **PACAP**: pituitary adenyl cyclase-activating peptide
- **PGE2**: prostaglandin E2
- **PKG:** protein kinase G
- **PTH:** parathyroid hormone.
- **PTHrP:** Parathyroid hormone-related peptide
- **REM**: rapid eye movement.
- **SDMA:** symmetrical dimethylarginine
- **SSRIs:** Selective serotonin reuptake inhibitor
- **T.P**.: total protein.
- **TG:** Triglycerides.
- **TLESR**: transient lower esophageal

• **ERA:** Electrical Response Activity. • **ESRD:** End stage renal disease. • **ET:** Endothelin. • **FBS:** fasting blood sugar. • **GEA:** Gastric Electric Activity • **GERD**: Gastroesophageal reflux disease. • **GPCRs**: G protein coupled receptors. • **GTP:** Guanosine Triphosphate. • **Hb:** hemoglobin. • **IBS**: irritable bowel disease. • **ICC:** interstitial cells of Cajal. • **IL 1:** interleukin 1 • **IL 6**: interleukin 6 • **INF**: interferon. • **iNOS**: inducble nitric oxide synthatase	sphincter relaxation. • **TNF**: tumor necrosis factor. • **UES:** upper esophageal sphincter. • **VIP:** Vasoactive Intestinal Peptide.

LISTS OF TABLES

LISTS OF FIGURES

INTRODUCTION AND AIM OF THE WORK

Upper Gastrointestinal (GI) discomfort such as anorexia, nausea, vomiting is a common feature of advanced renal failure. The exact cause of these symptoms is unclear, a contributing factor may be reduced gastric emptying resulting from autonomic dysfunction or a direct effect of Uremic toxins on gastric smooth muscles ***(Seoung W. et al., 2000).***

In chronic renal failure (CRF) patients both dialyzed and undialyzed, an abnormal gastric motility disorders are common, the pathogenesis seems to be multifactorial, and the presence of abdominal symptoms cannot foretell an abnormal motility disorder ***(Koa C.H. et al., 1996).***

Gastric motility is controlled by gastric myoelectrical activity, which propagates from the proximal body to the distal antrum at a frequency of 3-cycles/ minute ***(Seoung W. et al., 2000).*** Hemodialysis and Uremic patients experience such dyspeptic symptoms and there is higher prevalence of motility like disorders ***(Vanderwinden, 1999).***

Malnutrition affects between 13 and 20% of dialysis population, gastroparesis might be a cause of malnutrition and parameters of gastric emptying are inversely related with serum albumin level. Serum albumin level inversely correlates with overall motility in HD patients ***(Bruno et al., 2000).***

Nitric oxide (NO) is a gaseous biological messenger molecule that has been found to play a fundamental regulatory role in the body, it is involved in cardiovascular, immune, reproductive and digestive physiology. NO plays a central role in the physiology of GIT. Potential sources of NO in gut include: intrinsic intestinal tissue (mast cells, endothelium, smooth muscles, neuronal plexus, resident and or infiltrating leucocytes), NO acts as a neurotransmitter in the nervous system and other parts of the body. It is a potent vasodilator and cytoprotective substance, in gut it is involved in splanchnic and systemic hemodynamic regulation and it is acting as an inhibitory non-adrenergic, non-cholenergic neurotransmitter and relaxant of smooth muscles of GIT ***(Vanderwinden, 1999).***

Vasoactive intestinal peptide (VIP) contains 28 amino acid residues, it is found in nerves of gastrointestinal tract. In intestine it markedly stimulates intestinal secretion of electrolytes and hence water. Its other actions include

relaxation of gastric and intestinal smooth muscles including sphincters and inhibition of gastric secretions ***(William F. and Ganong, 1993).***

VIP is one of the neuropeptides which have recently shown to be neurotransmitter in the non-adrenergic, non- cholenergic inhibitory and excitatory nerves in human gut, where peptidergic nerves plays an important role in the impaired gastric motility ***(Tomita et al., 1999).***

Aim of the work:

The aim is to study the role of nitric oxide and vasoactive intestinal peptide on gastro-esophageal motility in chronic renal failure patients.

REVIEW OF LITERATURE