Comparative Study between the Urodynamic Effects of Anti-muscarinic Drugs and the Possible Urodynamic Effects of Nicorandil and Carbamazepine on Over Active Bladder Induced By Type-1 Diabetes Mellitus [Experimental and Clinical Study]

Thesis
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Abstract

Background: Overactive bladder (OAB) is a common clinical problem.

Materials and methods: **Experimental study:** seventy two adult male albino rats weighing 250-300 g, were classified into six groups. Blood glucose, cystometry, dose concentration response to Ach and histopathological examination were done.**Clinical Study**: The study was conducted on fifty with type-1 diabetes mellitus and over active bladder divided into five groups. Urodynamic studies were done and voiding diary and lower urinary symptom sheet was collected from each patient before and after treatment.

Results: **Experimental findings:** Diabetic rats exhibited a significant increase in the intravesical pressures, in tonic contractions to submaximal dose of ACh. and in bladder weight/body weight ratio and musculosa thickness compared to control group, while a significant reduction in those parameters were found in diabetic treated groups to diabetic group. For bladder volume, Oxybutinin and Tolterodine showed significant decrease while Nicorandil and Carbamazepine groups showed significant increase. **Clinical findings:** in Oxybutinin, Tolterodine groups urodynamic parameters and bladder capacities were significantly changed compared to placebo group while insignificant change were found in Nicorandil and Carbamazepine groups. *Conclusion: Carbamazepine* and *Nicorandil* potentially suppress the overactive bladder resulted from diabetes as shown in experimental work. On the other hand the clinical study didn't show a significant role for both drugs which needs further clinical trials with a more objective investigation.

Key words: Overactive bladder-Diabetes-Oxybutinin-Tolterodine-Carbamazepine-Nicorandil

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List of Abbreviations

+IWT: positive ice-water test

°C: celsius degree

5-HMT: 5-hydroxymethyl tolterodine

Ach: acetylcholine

AR: adrenergic receptor

ATP: adenosine triphosphate

BP: basal pressure

BPH: begnin prostatic hyperplasia

BTX: botulinum toxin

Ca^{2+}: calcium

cc: cubic centimeter

cGMP: cyclic guanine monophosphate

Cl: chloride

cmH_2O: centimeter water

CNS: central nervous system

CPGA: 2-cyclohexyl-2-phenylglycolic acid

CYP: cytochrome P

DBD: diabetic bladder dysfunction

DIU: sucrose-induced diuresis group

dl: deciliter

DM: diabetes mellitus

DNA: deoxyribonucleic acid

DRG: dorsal root ganglion

EC_{50}: submaximal concentration

ENaC: epithelial sodium channel

EP1: prostaglandin E receptor

ER: extended release

F: french

FD: first desire

FDA: food and drug administration

g: gram

h: hour

H^+: hydrogen

ICS: International Continence Society

IDDM: insulin dependent diabetes mellitus

IVP: intravesical pressure

IVPRs: intravesical pressure rises

K^+: potasium

Kg: kilogram

L: leakage

L: lumber

M: muscarinic

MCC: maximum cystometric capacity

Mg: magnesium

min: minute

ml: milliliter

mM: millimole

mmHg: millimeter mercury

MP: maximum pressure

NA: noradrenaline

Na^+: sodium

NAD^+: nicotinamide adenine dinucleotide

$NaH_2 PO_4$: sodium dihydrogen phosphate

$NaHCO_3$: sodium bicarbonate

NANC: non-adrenergic non-cholinergic

Na_V : voltage-gated Na^+ channels

ND: normal desire

NGF: nerve growth factor

NO: nitous oxide

OAB: overactive bladder

OTG: oxybutinin transdermal gel

Oxo: oxotremorine

P2X: ligand gated purine receptor

P2Y: G-protein bound purine receptor

p_{abd}: abdominal pressure

PAG: peri-aqueductal grey nucleus

p_{det}: detrusor pressure

PGs: prostaglandins

PMC: pontine micturition center

PSC: pontine urine storage center

p_{ves}: intravesical pressure

RTX: RTX: resiniferatoxin

s.c: subcutaneous

S: sacral

s: second

SCI: spinal cord injury

SD: standard deviation

SD: strong desire

SHR: spontaneous hypertensive rats

STZ: Streptozotocin

Th: thoracic

TP: threshold pressure

trKA: neurotrophic tyrosine kinase receptor type 1

TRP: transient receptor potential

TRPV1: transient receptor potential channel vanilloid type1

U: urgency

UD: urinary diversion group

ug: microgram

WKY: Wistar Kyoto

α: alpha

β: beta

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Introduction

Urinary bladder plays the major role in urine storage and voiding. Its functioning is regulated by the peripheral and central nervous system. Micturition starts with sensing bladder filling, transferring data to the central nervous system processing center and efferent pathways resulting in the voiding response. Increasing the volume of the urinary bladder provokes afferent signals to the central nervous system. The molecular basis of distention sensing involves the urothelium as a major factor during this process ***(Saeid and Ismail, 2010)***.

Bladder urothelium is the interface between the lumen of the urinary tract and underlying tissues. It forms an active participant in normal bladder function. It exists as an integral part of a sensory web, in which it communicates the degree of bladder filling to the underlying nervous and muscular tissues, and affects their function. This communication is made possible by the urothelial input and output pathways, which allow it to respond to its chemical and physical environment, and engage in multidirectional communication with neighboring cells in subadjacent tissues ***(Daneshgari et al., 2009).*** Bladder urothelial abnormalities may impact lower urinary tract function by altering the release of mediators and sensory fiber excitability in the bladder. Also, because many of these urothelial functions may be altered in diabetes cases, defects in urothelial cells may in part underlie changes such as detrusor instability and/or changes in bladder capacity ***(Hanna-Mitchell et al., 2013).***