

Comparative study of the effect of Diacerein and Diclofenac sodium and their combination in osteoarthritis model induced by monoiodoacetate in albino rats.

Thesis

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Abstract

Background and aim: Osteoarthritis (OA) is the most common joint disorder in the world. It is one of the most frequent causes of pain, loss of function and disability in adults. The current treatment of osteoarthritis is primarily focused on symptomatic relief by the use of rapidly acting analgesics such as NSAIDs and newer cyclooxygenase-2(COX-2) specific inhibitors that have many adverse effects. Hence, there is continuous search for new and better drugs for OA treatment. Interleukin-1 β plays an important role in the pathogenesis of OA. Diacerein, an Interleukin-1 β antagonist has been used recently in treatment of OA. Accordingly this work was designed to compare the anti-inflammatory effect of diacerein with one of the NSAIDs namely diclofenac sodium and their combination on animal model of osteoarthritis, and to study the effect of these drugs on systolic blood pressure.

Experimental approach: 90 adult healthy female albino rats were allocated into 5 groups: normal untreated animals (negative control), the disease model group that received a single dose of moniodoacetate (MIA) intra articularly in their right knees (positive control), and the (MIA) induced osteoarthritis treated either by diacerein, diclofenac sodium, or their combination for 6 weeks. Level of serum cartilage oligomeric matrix protein as a specific biochemical marker for cartilage, histopathologic examination, and radiological assessment were performed to evaluate the effect of the studied drugs. In addition a non-invasive measurement of systolic blood pressure was done to study the effect of these drugs on systolic blood pressure.

Results: Induction of OA by moniodoacetate (MIA) resulted in development of osteoarthritic changes detected by elevation of the biochemical parameter measured, deterioration of pathological scores and X-rays. Interestingly the administration of diacerein alone or with diclofenac sodium resulted in significant amelioration of all the parameters measured with no effect on systolic blood pressure. However, diacerein intake alone showed the best results.

Conclusion: The results of the present study revealed that diacerein has the potential to ameliorate osteoarthritic changes with no effect on the blood pressure unlike the commonly used NSAIDs.

Key words: Osteoarthritis, Diacerein, Diclofenac sodium, Moniodoacetate.

CONTENTS

	Page
Acknowledgement	i
Abstract	iii
List of Contents	iv
List of Abbreviation.....	vi
List of Tables	x
List of Figures	xi
List of photos	xii
 Introduction	 1
 Aim of the Work	 3
 Review of Literature	 4
– Osteoarthritis	
Prevalence and definition of osteoarthritis (OA).....	4
Risk factors of OA.....	5
Classification of OA.....	10
Structure of knee joints both normal and with osteoarthritis.....	10
Pathogenesis of OA.....	14
Theories for OA development.....	16
Diagnosis of OA.....	17
Management of OA.....	21
– Diclofenac sodium.....	23
– Diacerein.....	25
 Material and Methods	 28
○ Material	28
○ Methods	31
○ Statistical Analysis	39
 Results	 40

Discussion	87
Summary and conclusion	100
References	103
Arabic summary.....	

LIST OF ABBREVIATIONS

ACL:	Anterior cruciate ligament.
ACR:	American College of Rheumatology.
ADAMTS:	A disintegrin and metalloproteinase domain with thrombospondin.
ANOVA:	Analysis of variance.
AUC:	Area under the curve.
BIPED:	Burden of disease, Investigative, Prognostic, Efficacy, Diagnostic.
BJD:	Bone and Joint Decade.
BMI:	Body mass index
Cm:	Centimeter.
COMP:	Cartilage Oligomeric Matrix Protein.
COX-1:	Cyclooxygenase-1.
COX-2:	Cyclooxygenase-2.
CTX-II:	C-terminal telopeptide of type II collagen.
e.g:	example.
ECM:	Extra Cellular Matrix.
ELISA:	Enzyme-linked immunoabsorbant assay.
ERK:	Extracellular-signal-regulated kinase.

EULAR:	European League against Rheumatism.
F.F.D:	Focal Film Distance.
Fig:	Figure.
Gm:	gram.
H&E:	Hematoxylin and Eosin.
hr:	hour.
I.M:	Intramuscular.
ICE:	Interlukin-1 converting enzyme.
IL-1 β :	Interleukin-1beta.
IL-1R:	Interleukin-1 receptor.
IL-1ra:	Interleukin-1 receptor antagonist.
IL-6:	Interleukin-6.
IL-8:	Interleukin-8.
I κ B:	nuclear factor kappa B (NF- κ B) inhibitor.
Kg:	Kilogram.
KSS:	Knee society score
KVP:	kilo volt potential.
L:	Liter.
LII:	Lequesne impairment index

Lt:	Left.
mAs:	mille Ampere.
MEK:	mitogen-activated protein kinase (MAPkinase).
mg:	milligram.
MIA:	Monoiodoacetate.
ml:	milliliter.
Mm:	millimeter
MMP:	Matrix Metalloproteinase.
MRI:	Magnetic Resonance Image.
NF- κ B:	Nuclear factor-kappa B.
ng:	nanogram
NO:	Nitric oxide.
NSAIDs:	Non-steroidal anti-inflammatory drugs.
OA:	Osteoarthritis.
PGs:	Prostaglandins
PGE2:	Prostaglandin E2.
Pg/ml:	pictogram per milliliter.
ROS:	Reactive oxygen species.
Rt:	Right.

SBP:	systolic blood pressure.
SD:	Standard deviation.
SR:	Sustained release.
SYSADOA:	Symptomatic Slow Acting Drug in OA.
T _{1/2} :	half-life.
TGF- β :	Transforming growth factor β .
TIMP:	Tissue inhibitors of metalloproteinase.
TNF- α :	Tumor necrosis factor –alpha
US:	United States.
VAS:	Visual analogue scale
WHO:	World Health Organization
W:	week.
μ l:	micro liter.

List of Tables

Page

Table (1): Changes in serum COMP level (pg/ml) in normal control group versus MIA induced OA group at 2 nd , 4 th and 6 th weeks after OA induction.....	46
Table (2): Average pathological scoring of normal control group versus MIA induced OA group at 2 nd , 4 th , 6 th weeks.....	50
Table (3): Changes in serum COMP level (pg/ml) in MIA induced OA group (IIA) versus diacerein treated OA group (IIB) at 2 nd , 4 th and 6 th weeks after OA induction.....	53
Table (4): Average pathological scoring of MIA induced OA group (IIA) and diacerein treated OA group (IIB) at 2 nd , 4 th , 6 th weeks.....	57
Table (5): Changes in serum COMP level (pg/ml) in MIA induced OA group (IIA) versus diclofenac treated OA group (IIC) at 2 nd , 4 th and 6 th weeks after OA induction.....	61
Table (6): Average pathological scoring of MIA induced OA group (IIA) and diclofenac treated OA group (IIC) at 2 nd , 4 th and 6 th weeks.....	65
Table (7): Changes in serum COMP level (pg/ml) in MIA induced OA group (IIA) versus combination of diacerein and diclofenac treated OA group (IID) at 2 nd , 4 th and 6 th weeks after OA induction.....	68
Table (8): Average pathological scoring of MIA induced OA group (IIA) and combination of diacerein with diclofenac OA treated group (IID) at 2 nd , 4 th and 6 th weeks.....	72
Table (9): Changes in serum COMP level (pg/ml) in osteoarthritis untreated model group (IIA) versus the disease model groups receiving either diacerein (IIB), diclofenac (IIC) or their combination (IID).....	75
Table (10): Changes in mean serum COMP level (pg/ml) in each group measured at 2 nd , 4 th and 6 th weeks (repeated measures ANOVA).....	77
Table (11): Serum COMP % change of osteoarthritic untreated model group (IIA) versus OA groups receiving either diacerein (IIB), diclofenac (IIC) or their combination (IID).....	78
Table (12): Average pathological scoring of osteoarthritis untreated model group (IIA) and OA groups receiving either diacerein (IIB), diclofenac (IIC) or their combination (IID).....	80
Table (13): Changes in average pathological scoring at 2 nd , 4 th and 6 th weeks in each group (repeated measures ANOVA).....	81
Table (14): Systolic blood pressure readings (mmHg) in normal control group (I), MIA induced OA model group (IIA), diacerein treated OA group (IIB), diclofenac treated OA group (IIC) and diacerein with diclofenac treated OA group (IID).....	84

List of Figures

Page

Figure (1): Schematic representation of relations between environmental and endogenous risk factors for OA.....	6
Figure (2): The four zones of cartilage.....	11
Figure (3): Normal structure of knee (Lt) and the pathologic changes observed in OA joint (Rt).....	13
Figure (4): Schematic of pathogenic mechanisms of osteoarthritis.....	15
Figure (5): Progress of OA along time, different modalities of its diagnosis, stages of osteoarthritis and suggested methods of their detection.....	17
Figure (6): Medial side OA of knee joint	20
Figure (7): Effect of diacerein/rhein on the IL-1 system.....	27
Figure (8): Changes in serum COMP level (pg/ml) in normal control group versus MIA induced OA group at 2 nd , 4 th and 6 th weeks after OA induction	47
Figure (9): Changes in serum COMP level (pg/ml) in MIA induced OA group (IIA) versus diacerein treated OA group (IIB) at 2 nd , 4 th and 6 th weeks after OA induction	54
Figure (10): Changes in serum COMP level (pg/ml) in MIA induced OA group (IIA) versus diclofenac treated OA group (IIC) at 2 nd , 4 th and 6 th weeks after OA induction	61
Figure (11): Changes in serum COMP level (pg/ml) in MIA induced OA group (IIA) versus combination of diacerein and diclofenac treated OA group (IID) at 2 nd , 4 th and 6 th weeks after OA induction	69
Figure (12): Changes in serum COMP level (pg/ml) in osteoarthritis untreated model group (IIA) versus the disease model groups receiving either diacerein (IIB), diclofenac (IIC) or their combination (IID).....	76
Figure (13): Differences between average histopathological scoring of animal groups (normal control, MIA induced OA, diacerein treated OA, diclofenac treated OA and combination of diacerein with diclofenac treated OA groups) in the three consecutive durations (2 nd , 4 th and 6 th weeks).....	82
Figure (14): Systolic blood pressure readings (mmHg) in normal control, MIA induced OA model, diacerein treated OA, diclofenac treated OA and diacerein with diclofenac treated OA groups.....	84
Figure (15): Systolic blood pressure readings in rats of A: normal control, B: disease model of OA induced by MIA, C: diacerein treated OA for 6 weeks, D: diclofenac treated OA for 6 weeks, E: combination of diacerein and diclofenac treated OA for 6 weeks.....	85

List of Photos

Page

Photo (1): Light photomicrographs of rat's right knee joint from group I (negative control group).....	42
Photo (2): Radiograph of normal rat's knee joint.....	43
Photo (3): Light photomicrograph of rat's right knee joint from group IIA (MIA induced OA model) at 2 weeks.....	48
Photo (4): Light photomicrograph of rat's right knee joint from group IIA (MIA induced OA model) at 4 weeks.....	48
Photo (5): Light photomicrograph of rat's right knee joint from group IIA (MIA induced OA model) at 6 weeks.....	49
Photo (6): Radiographic changes in rat's right knee joint in untreated OA model group (IIA) at 2weeks (a), 4 weeks (e) and 6 weeks (i) after OA induction.....	50
Photo (7): Light photomicrograph of rat's right knee joint from group IIB (diacerein treated OA group) at 2 weeks.....	55
Photo (8): Light photomicrograph of rat's right knee joint from group IIB (diacerein treated OA group) at 4 weeks.....	55
Photo (9): Light photomicrograph of rat's right knee joint from group IIB (diacerein treated OA group) at 6 weeks.....	56
Photo (10): Radiographic changes in rat's right knee joints in (diacerein treated OA group (IIB) at 2weeks (c), 4 weeks (g) and 6 weeks (k) after OA induction.....	58
Photo (11): Light photomicrograph of rat's right knee joint from group IIC (diclofenac treated OA group) at 2 weeks.....	62
Photo (12): Light photomicrograph of rat's right knee joint from group IIC (diclofenac treated OA group) at 4 weeks.....	63
Photo (13): Light photomicrograph of rat's right knee joint from group IIC (diclofenac treated OA group) at 6 weeks.....	64
Photo (14): Radiographic changes in rat's right knee joints in diclofenac treated OA group (IIC) at 2weeks (b), 4 weeks (f) and 6 weeks (j) after OA induction.....	65

Photo (15): Light photomicrograph of rat's right knee joint from group IID (combination of diacerein and diclofenac OA treated group) at 2 weeks.....	70
Photo (16): Light photomicrograph of rat's right knee joint from group IID (combination of diacerein and diclofenac OA treated group) at 4 weeks.....	70
Photo (17): Light photomicrograph of rat's right knee joint from group IID (combination of diacerein and diclofenac OA treated group) at 6 weeks.....	71
Photo (18): Radiographic changes in rat's right knee joint in combination of diacerein and diclofenac treated OA group (IID) at 2 nd , 4 th and 6 th weeks after OA induction.....	73

Introduction

Osteoarthritis was considered for many years as a non-inflammatory condition affecting the joint. Later, it was found that some sort of inflammation occurs in the joint which cause the pathological changes that precede the pain, which is the most striking complaint in a patient with OA, making him seek medical advice (**Brandt et al., 2008**). Although non steroidal anti inflammatory drugs (NSAIDs) play a major role in relieving the process of inflammation in many disorders in medicine, (**Colville-Nash and Willoughby, 2002; Boileau et al., 2008**) stated that their effectiveness in disease control mainly through their analgesic action rather than their anti-inflammatory effect.

OA patients are usually of a senior age, suffering from reduction in the function of various organ systems. Non-steroidal anti-inflammatory drugs (NSAIDs) and COX-2 inhibitors are associated with high rates of adverse events (e.g., gastrointestinal, cardiovascular, renal) especially in older patients. In addition, there is an analgesic ceiling effect of NSAIDs, at which efficacy plateau occurs despite increasing the doses (**Steinmeyer and Kontinen, 2006**). All these facts can render increasing the NSAIDs dose inappropriate for the management of painful OA flare (**Felson et al., 2000**).

The economic costs of OA are high. They include those related to treatment for patients and for their families who must adapt their lives and homes to the requirement of the disease, and those due to loss of work and productivity (**Altman, 2010**). At present, there are no therapies proven to arrest or decrease the progress of the disease process, and therefore in some individuals, OA may require hip or knee joint replacement (**Martel-Pelletier and Pelletier (a), 2010**).